

Lund 1975

Clinical and Experimental
Studies on
Vesico-Ureteric Reflux

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Studies on
Vesico-Ureteric Reflux

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To U.

"The light which experience gives is a
lantern on the stern, which shines
only on the waves behind us".

SAMUEL T COLERIDGE (1772-1834)

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CLINICAL AND EXPERIMENTAL STUDIES ON

VESICO-URETERIC REFLUX

by

INGEMAR HELIN

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- I. HELIN, I., OKMIAN, L., KORNFÄLT, S.Å. & MORTENSSON, W.: Vesico-ureteric reflux in children. I. A therapeutical approach and a prospective study. Z Kinderchir 15:299 - 312, 1974
- II. MORTENSSON, W. & HELIN, I.: Vesico-ureteric reflux in children. II. Roentgenologic examination. Z Kinderchir 15:444 - 454, 1974
- III. HELIN, I., OKMIAN, L. & OLIN, T.: Renal blood flow and function during neuroleptanaesthesia and at elevated intravesical pressure. An experimental study in the pig. To appear in Scand J Urol Nephrol
- IV. HELIN, I., OKMIAN, L. & OLIN, T.: Renal blood flow and function at elevated ureteric pressure. An experimental study in the pig. To appear in Scand J Urol Nephrol
- V. HELIN, I., OKMIAN, L. & OLIN, T.: Renal blood flow and function in vesico-ureteric reflux. An experimental study in the pig. To appear in Scand J Urol Nephrol

Reference to these papers will be made by Roman numerals.

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INTRODUCTION

As early as 150 A.D., Galen was able to demonstrate that reflux of urine from the bladder to the ureters did not normally occur. Semblinow (1883) was the first to demonstrate vesico-ureteric reflux in animal experiments and, ten years later, Pozzi (1893) reported regurgitation of urine in man when he mistakenly severed the ureter at hysterectomy. At the turn of the century, Lewin & Goldschmidt (1898) showed that in rabbits methylene blue could reach the kidney from the bladder. Young (1898) and Sampson (1903) were unable to substantiate this finding in experiments on human and canine cadavers, even when high intravesical pressures were applied, whereas Courtade & Guyon (1894) and Graves & Davidoff (1923) reported a high percentage of spontaneous reflux in dogs as well as in rabbits. In 1929, Gruber established that a poor development of the trigone was responsible for the higher frequency of reflux in some species. In a comparative study of different animals, he also determined that, as a rule, the vesico-ureteric junction is competent in the pig, due to a long intravesical ureter. Later Auer & Seager (1937) established in animals that local oedema around the ureteric orifice could give rise to vesico-ureteric reflux that disappeared when the oedema subsided. Observations in animal experiments cannot, however, be transferred to humans without further ado. Although the first cystography was performed by Wulff in 1905, it was not until in 1924 that Bumpus used this technique to point out a direct relationship between urinary tract infection and vesico-ureteric reflux. The results of laborious experimental and clinical investigations were not fully acknowledged in clinical praxis. Hutch & Amar (1972) consider the thirties and forties to be silent years as regards studies on vesico-ureteric reflux.

The oblique course of the ureter through the bladder wall was documented on microphotos by Sampson (1903). The intravesical ureter has been thoroughly dissected by Satani (1919), Hutch et al (1961), Tanagho & Pugh (1963), Tanagho & Smith (1966), who have determined that the trigone is the only distal point of attachment of the ureter. Under normal conditions,

the tone and contractility of the uretero-trigonal muscles are responsible for the closure of the ureteric orifice. The terminal ureter is furthermore surrounded by a thin layer of muscle from the ureteral adventita, which runs longitudinally to connect the ureter with the bladder wall. It is considered to prevent reflux during micturition by actively contracting and closing the intravesical ureter (Hutch & Amar, 1972).

Known anatomical facts and assumed mechanism of function govern the techniques for operative repair of vesico-ureteric reflux. Exact surgical duplication of normal structures is impossible, but it is essential to get as close as possible in order to achieve the same function. Tanagho (1970) has pointed out that the basic approaches to anatomical reconstruction are the procedures described by Politano & Leadbetter (1958) and Paquin (1959).

Since most cases of reflux occur in conjunction with urinary tract infection, it is difficult to distinguish the effects of the reflux itself from those of the infection. Only a few investigators have studied the effect of reflux on kidneys in the absence of urinary tract infection. Fritjofsson & Sundin (1966) found intact renal function in adult patients with reflux but without infection. Their findings were substantiated in animal experiments by King & Idriss (1967) and Lenaghan et al (1972). On the other hand, Rowland et al (1960) reported decreased renal function in cord injury patients with vesico-ureteric reflux, without any direct relationship to past urinary tract infections, and Hutch & Smith (1969) stated that "reflux damages the kidney by infection and by hydrostatic effects of refluxed urine".

It has been established that irreversible vesico-ureteric reflux results from congenital defects of the vesico-ureteric junction (primary VUR). It has also been shown that urinary tract infection may cause reversible vesico-ureteric reflux (secondary VUR), and that children with VUR are more frequently exposed to urinary tract infection (UTI) than those without. The choice of appropriate treatment - operation

or prolonged chemoprophylaxis - is further complicated by the fact that an insufficient vesico-ureteric junction can become sufficient during the growth of the child.

AIM OF THE PRESENT STUDY

The current clinical approach is to attempt to differentiate the diagnosis and treatment of VUR, in accordance with the considerations mentioned above, by the aid of endoscopy, micturition urethrocystography and urography. The purpose of the clinical studies (I, II) was to assess the outcome of this approach in a three-year material.

In VUR the kidneys are exposed to ascending infections and the urodynamic effects of refluxed urine. The irreversible effects of recurrent pyelonephritis are well-known. In dealing with patients with VUR it is therefore a prerequisite to prevent UTI so that the vesico-ureteric junction will have suitable conditions to grow and the reflux to disappear. Another prerequisite is that, in the meantime, the urodynamic effects of VUR on the kidney are small or reversible. This raises the question of whether or not a sterile VUR interferes with renal function. An experimental study was undertaken to judge this point (V).

In order to judge the results of that study, it became necessary to determine the effects on the registered renal parameters of the anaesthesia used and of elevation of the intravesical pressure (III). Finally, the effects of elevating the ureteric pressure in the absence of VUR had also to be considered (IV).

CLINICAL INVESTIGATIONS (I, II)

Material and methods

The series included 104 children with reflux in 145 ureters. The material was limited to comprise vesico-ureteric reflux (VUR) of congenital origin and VUR secondary to non-obstructive urinary tract infection (UTI). The reason for admittance of 72 children was recurrent UTI, whereas 20 revealed a history of one attack of acute pyelonephritis. Enuresis, albuminuria, haematuria and minor urological complaints were reasons for the admittance of the remaining 12 patients. The onset of symptoms appeared before four years of age in 85 of the patients.

The therapeutical approach was based upon an effort to achieve early differentiation between primary and secondary reflux, followed by the operative treatment of primary VUR and prolonged chemoprophylaxis of secondary VUR.

Endoscopy was used to examine the ureteric orifices with regard to their size, shape and peristaltic activity as well as their mutual positions within the trigone. Catheterization of the distal ureter was performed to evaluate the length and course of the intravesical ureter. An intravesical length of at least 0.3 cm in a newborn child, 0.5 cm in a one year old child and 0.8 cm in children up to ten years of age was regarded as normal.

Standardized micturition urethrocystography was used to diagnose and classify reflux into free reflux and reflux on micturition. In order to demonstrate the possible occurrence of free reflux, the bladder was filled with contrast medium (Isopaque Cysto, 100 mgI/ml, sodium metrizoate, Nyegaard A/S, Norway) until the intravesical pressure came into equilibrium with a pressure of 25 cm H₂O. Reflux grade 1 means that the contrast medium goes up into the ureter but does not reach the renal pelvis. At reflux grade 2 the pelvis is also filled and at reflux grade 3 the

upper urinary tract is distended to a varying degree. Distension in this context means that the upper urinary tract is wider than at urography without abdominal compression.

At urography the renal scarring was minutely examined and a renal size index determined to estimate the amount of renal tissue. The long axis of the kidney, as measured on the roentgen film, was expressed as a percentage of the distance from the upper border of the first lumbar vertebra to the lower border of the fourth.

Chemoprophylaxis was given to all patients awaiting operation and six months postoperatively, and to those designated to long-term prophylaxis against UTI. Nitrofurantoin (Nitrofurantoinum NFN) in a dose of 3 mg/kg body-weight and day, divided into two doses, was the usual treatment.

The operative procedure was in accordance with the technique described by Politano & Leadbetter (1958), with the exception that the distal one to two cm of the ureter were resected.

RESULTS

A total of 63 patients with in all 92 refluxing ureters underwent operative treatment. Eighty-one of these ureters were examined by endoscopy, and the endoscopic and operative findings could be minutely compared in 65 ureters. At endoscopy, 24 ureters were found to have no demonstrable submucosal part, and this was verified in all of them at operation. A short submucosal tunnel was revealed by endoscopy in another 24 ureters, but in seven of these no submucosal part could be seen at operation. Out of 17 ureters in which endoscopy demonstrated a normal tunnel, seven were found to have no tunnel at operation, whereas three had a short one. Micturition urethrocytography revealed no relation between the length of the submucosal tunnel and the occurrence of free reflux. The degree of reflux, both free and on micturition did, however, show a tendency to be less marked if the submucosal segment was of normal length.

All the 63 operated patients were given chemoprophylaxis for six months postoperatively and followed with regular controls of urinary specimens every month for another six months.

In the 41 non-operated children, reflux in 53 ureters disappeared during chemoprophylaxis against UTI; within one year in 36 ureters and within two years in the remaining 17. At endoscopy, 48 of these refluxing ureters were assessed by inspection and catheterization. Only one of them was considered to have no visible submucosal tunnel. Thirty of the 53 ureters were tested for the occurrence of free reflux and this was demonstrated in seven of them.

In this study, 92 of the 104 children were referred because of UTI. When the VUR had disappeared, only four children in the operative group and six in the non-operative group developed UTI during a period of six months after the prophylaxis had been withdrawn.

The renal size index was inversely proportional to the degree of VUR. Kidneys exposed to reflux and with distension of the upper urinary tract were significantly smaller than those without reflux.

Pyelonephritic changes were more marked and occurred more frequently in patients with marked reflux on micturition. This seemed not to be influenced by the presence or absence of free reflux. As the entire group of children received chemoprophylaxis to prevent UTI, it could be established that pyelonephritic changes seldom appeared or progressed when chemoprophylaxis had been started.

As to the prognosis of VUR, it was found that the combination of free reflux and marked reflux on micturition rendered it less probable that the reflux would disappear spontaneously.

At the first postoperative urography, performed one week after the operation, there was usually dilatation of the ureter and renal pelvis on the operated side. The dilatation had commonly disappeared at the control about one month later.

Pyelonephritic changes never occurred during one year of postoperative follow-up in kidneys that were normal prior to operation. In two patients, renal scarring which had started preoperatively progressed after the operation.

In the 41 children with VUR that disappeared on chemoprophylaxis only, pyelonephritic changes appeared in four kidneys during the observation period. In seven kidneys parenchymal changes were present at the first examination and did not progress during the observation period.

At the final control with micturition urethrocystography one year after the operation, 90 of the 92 operated ureters were free of reflux. In two patients a distal ureteric stenosis appeared more than one year after the operation, calling for re-operation in one patient.

EXPERIMENTAL INVESTIGATIONS (III, IV and V).

Material and methods

Twenty-three piglets of the Swedish Land race were used. Anaesthesia was obtained with ketamine hydrochloride (Ketaminum NFN) and droperidole (Droperidolum INN), supplemented with alcuronium chloride (Alcuronium NFN) as a muscle relaxant. All the animals were intubated and ventilated by a respirator with a mixture of 33 per cent O_2 , 66 per cent N_2 and one per cent CO_2 . Adjustments of the ventilation were made if indicated by changes in P_{O_2} or the acid-base balance (P_{CO_2} , pH, standard bicarbonate and base excess). In all animals the body temperature was kept almost constant by insulation and an electric heating pad.

To measure renal blood flow the renal artery was catheterized with a radio-opaque catheter via the femoral artery, and the corresponding vein was catheterized via the femoral vein. The position of the catheters was checked by injecting small amounts of roentgen contrast medium during magnification fluoroscopy. When not in use for blood flow measurements, the catheters were connected to an electromanometer for determination of the arterial and venous blood pressures.

When measuring renal blood flow, indocyanine green solution was injected into the renal artery. Simultaneously, blood was withdrawn from the corresponding vein and passed through a spectrophotometer cuvette at a rate of 0.5 ml/sec. Continuous registration of the dye concentration in the renal venous blood was effected on a potentiometer recorder. The area of the excised curve was measured and the blood flow calculated as described by Lingårdh et al (1969).

When measuring cardiac output, dye solution was injected into one of the renal veins and arterial blood continuously sampled at a rate of 0.5 ml/sec. The flow was calculated as above and the renal fraction of the cardiac output determined.

As clearance techniques usually require catheterization of the ureters, they cannot be applied during experiments involving urinary stasis. It is, however, possible to evaluate glomerular and tubular function by determining the extraction capacities for labelled EDTA and Hippuran. These radionuclides were infused intravenously at a constant rate throughout the experiments. After each blood flow determination had been completed, samples were withdrawn from the renal artery and corresponding vein and counted in an automatic well crystal scintillation detector. The extraction was calculated after corrections had been made for background count and overlap between the radionuclides.

The mean arterial blood pressure was calculated as the diastolic pressure plus one-third of the pulse pressure.

Renal vascular resistance was calculated in the conventional fashion (Lyrdal & Olin, 1974) with correction for the venous pressure.

Glomerular filtration rate was expressed as the clearance of ^{51}Cr -EDTA.

Renal blood flow and function during neuroleptanaesthesia and at elevated intravesical pressure (III).

The effects on renal blood flow and function of neuroleptanaesthesia alone were studied in five piglets. The renal circulatory and functional parameters were recorded every 30 minutes for two hours.

In a second group of seven piglets under neuroleptanaesthesia, the intravesical pressure was successively elevated to 10, 25, 50 and 75 mm Hg. The renal circulatory and functional parameters were recorded when the intravesical pressure was in equilibrium with a bottle containing physiological saline at heights over the bladder corresponding to the pressure required.

Renal blood flow and function at elevated ureteric pressure (IV)

Five piglets were used. Initial measurements of renal blood flow and function were made on both sides with free urinary flow through the catheterized ureter. Thereafter, the measurements were repeated bilaterally at unilateral ureteric pressures of 10, 25, 50 and 75 mm Hg. Thus the contralateral kidney served as a control.

Renal blood flow and function in vesico-ureteric reflux (V)

In six piglets, weighing 4.3 to 4.8 kg, free vesico-ureteric reflux was created by suprapubic longitudinal transection of one of the vesico-ureteric junctions. Three months later, when the animals weighed about 40 kg, renal blood flow and function were studied bilaterally at intravesical pressures of 10, 25, 50 and 75 mm Hg. The contralateral kidney served as a control.

RESULTS

Renal blood flow and function during neuroleptanaesthesia and at elevated intravesical pressure (III)

During neuroleptanaesthesia only minor fluctuations in renal blood flow (RBF) were seen. The mean renal fraction of the cardiac output ($\text{RBF \% CO}$) also remained fairly stable. Significant changes in the renal vascular resistance (RVR) and the mean arterial blood pressure (MABP) paralleled each other. The mean venous blood pressure (MVBP) was unaffected. The extraction of EDTA (E_{EDTA}) showed insignificant variations, whereas the extraction of Hippuran (E_{Hipp}) fell continuously during the study. The estimated glomerular filtration rate (GFR) as a rule followed changes in E_{EDTA} . When the intravesical pressure was elevated in addition, RVR increased significantly, paralleled by a slight increase of MABP. RBF, $\text{RBF \% CO}$ and MVBP were fairly stable. The extraction of EDTA and Hippuran fell progressively, with the main decrease occurring at intravesical pressures of

50 and 75 mm Hg. The reduction in E_{EDTA} was paralleled by a decrease in GFR.

Urinary tract infection did not appear in any of the animals. Haematocrit, P_{O_2} , and acid-base balance were unchanged during the experiments.

Renal blood flow and function at elevated ureteric pressure (IV)

The unilateral ureteric pressure increase caused no significant changes in RBF or $\text{RBF \% CO}$ in any of the kidneys. RVR decreased bilaterally at a unilateral ureteric pressure of 10 mm Hg. As a rule the variations were insignificant, but there was a tendency for RVR in the experimental kidney to increase when the ureteric pressure was elevated. MABP and MVBP exhibited only minor, insignificant fluctuations. E_{EDTA} and E_{Hipp} decreased successively when the pressure in the corresponding ureter was elevated. Contralaterally, irregular variations were recorded in the extraction of both substances. GFR diminished significantly in the kidney subjected to elevated ureteric pressure, whereas contralaterally fluctuations similar to those for E_{EDTA} were seen.

The specimens of urine were normal in all animals, as were P_{O_2} and the acid-base balance.

Renal blood flow and function in vesico-ureteric reflux (V)

In kidneys that had been subjected to a free and uninfected reflux for three months, RBF showed significant changes when the intravesical pressure was elevated. Contralaterally, RBF showed only minor, insignificant variations. In the experimental kidney, variations in $\text{RBF \% CO}$ followed the same pattern as those in RBF . Contralaterally, $\text{RBF \% CO}$ was fairly constant. Apart from a slight decrease in RVR in the experimental kidney at an intravesical pressure of 10 mm Hg, RVR generally increased bilaterally. Only minor fluctuations were recorded in MABP and MVBP . In kidneys subjected to free reflux, initial values for E_{EDTA}

and E_{Hipp} were about 50 per cent lower than normal. During elevation of the intravesical pressure, E_{EDTA} and E_{Hipp} decreased significantly in both kidneys. In the control kidney the decrease occurred mainly at intravesical pressures of 50 and 75 mm Hg, whereas in the experimental kidney a decrease was already noticeable at a pressure of 10 mm Hg. GFR was also significantly reduced bilaterally, but the reduction was more accentuated in kidneys subjected to reflux. The initial values for GFR were reduced by 50 per cent in these kidneys.

None of the animals developed a urinary tract infection during the period of reflux. P_{O_2} and the acid-base balance were stable during the experiments.

GENERAL DISCUSSION

The primary goal of a surgical procedure in vesico-ureteric reflux is to preserve renal function by eliminating the risk of ascending infections. There is, however, no general agreement as to how to select patients for operation and therefore most urologists have developed their own criteria and guiding principles. In recent years, indications for operative treatment of children with vesico-ureteric reflux have been discussed in the literature (Bettex, 1970; Hutch & Amar, 1974; Scott, 1969 and Seiferth et al, 1974). Most authors agree that in certain types of vesico-ureteric reflux there is no possibility of spontaneous normalization. These include congenital anomaly of the ureteric orifice, ureteric duplication and ureteric ectopia and bladder diverticulum with the ureter opening into the bottom of the diverticulum. In other cases, dilatation of the upper urinary tract is present, and operative treatment favoured if the dilatation is already pronounced at the first roentgen examination or progresses during the follow-up (Hutch & Amar, 1972; Scott, 1969). The response to chemoprophylaxis has also to be considered. If urinary tract infections cannot be prevented, surgical correction of the reflux must be undertaken in order to avert renal damage (Bettex, 1970; and others).

Our therapeutical approach was based upon an effort to achieve an early differentiation into primary and secondary vesico-ureteric reflux, followed by operative treatment of primary reflux and prolonged chemoprophylaxis of secondary reflux. When no clear-cut, reliable diagnosis could be obtained, long-term chemoprophylaxis was chosen as a means of attempting differentiation. In addition, at least two weeks' absence of urinary tract infection was considered a prerequisite for operative treatment.

Early operative treatment was undertaken in 22 patients. In some of these, the indications were those mentioned above, in others special conditions called for operation: operative treatment was chosen to ensure protection of a solitary kidney with reflux, and in patients with severely impaired renal function. In the latter instance, the risk of effluent blockage was considered smaller than that of further impairment of the renal function.

The remaining 82 patients were initially assigned chemoprophylaxis alone to prevent urinary tract infection and give the vesico-ureteric junction a chance to normalize. Half of them were rid of their reflux within two years of chemoprophylaxis, whereas 12 had to be operated upon during this period, due to unchanged or progressive dilatation of the upper urinary tract, impaired renal function, or lately confirmed anomalies. After two years of chemoprophylaxis, 29 patients still presented with reflux. It was considered that chemoprophylaxis had prevented urinary tract infections for such a long time in these cases that the reflux ought to have disappeared if it was due to secondary changes at the vesico-ureteric junction. The reflux was therefore classified as irreversible and operative treatment was undertaken.

The degree of reflux usually indicates the extent of incompetency of the vesico-ureteric junction, free reflux pointing to greater incompetency than reflux only on micturition. The risk of ascending infection is, however, the same. In dealing with our patients, endoscopy including catheterization of the distal ureter proved valuable, particularly as regarded ureters with a perpendicular course through the bladder wall. If the ureter followed a submucosal course to a certain degree it proved difficult to judge the endoscopical findings with certainty. This was attributed to optical phenomena, including the degree of magnification and the distorsion of perspective obtained. The extent of filling of the bladder may also have provided a source of error, as the ureteric orifices were judged first with the bladder empty and then at an intravesical pressure of 30 mm Hg. The results of a carefully performed endoscopy did, however, provide reliable clues about abnormal ureteric orifices. Out of 58 orifices found to be abnormal at operation, 48 had already been judged to be so at endoscopy. The risk of overdiagnosing abnormal ureteric orifices with the technique used is considered to be small.

In assessing a vesico-ureteric reflux, micturition urethrocystography did not prove as valuable as had been expected. The occurrence of free

reflux could not be closely correlated to the absence of a submucosal segment. Obviously certain virulent urinary tract infections may cause a total incompetency of the vesico-ureteric junction and concomitant free reflux. However, there was a tendency for the reflux to be less marked if the submucosal tunnel was of normal length. It is difficult to evaluate the width of the ureter in children with reflux as the renal pelvis and the ureter can easily be distended. Distension during micturition is also dependant upon the intravesical pressure. It must therefore be considered rather unsuitable to use dilatation of the upper urinary tract, as measured at micturition urethrocytography, as the only decisive factor in the selection of patients for operation.

Urography gave information about the extent of renal parenchymal changes. Pylonephritic changes were more extensive and occurred more frequently in cases with marked reflux on micturition, but they seemed not to be influenced by the presence or absence of free reflux. This may imply that a reflux appearing only at a high intravesical pressure can be a contributory factor in the production of renal scarring.

The results of the therapeutical approach stress the fact that it still is difficult to establish permanent rules for dealing with patients with vesico-ureteric reflux. The information gained by a carefully performed endoscopy, including catheterization of the terminal ureteric course, is nevertheless of great value in the differentiation between primary and secondary reflux. In doubtful cases, in which endoscopy reveals a subnormal length of the submucosal tunnel, chemoprophylaxis against urinary tract infections ought to be chosen in preference to operation, especially in children under three years of age. We chose two years as a suitable period for the children to recover from their reflux. The urine was sterile throughout this period. This was ensured by careful dosage with Nitrofurantoin with respect to the body-weight.

If it is chosen to await the disappearance of a vesico-ureteric reflux, it is a prerequisite that the urodynamic effects of refluxed urine on the renal function are negligible or reversible. When investigating this

in the growing animal, it was found that a long-term, free and sterile reflux caused a decrease in glomerular and tubular function of about 50 per cent. It seems possible that the column of urine that is regurgitated again and again to the renal pelvis is responsible for this decrease. The changes may be reversible but, as no operative treatment of the reflux was undertaken, this supposition could not be judged. At interference with the renal blood flow was registered when the intravesical and, consequently, the ureteric pressure was elevated in animals with reflux. This susceptibility to change must have been due to the existence of a long-term reflux as no changes were observed when the intravesical (III) or ureteric (IV) pressures were elevated without pre-existing reflux. Even if a sterile reflux certainly is less damaging to the kidney than an infected reflux, these investigations have demonstrated that sterile reflux alone is harmful to the kidney in the growing animal due to its urodynamic effects. This has been suggested to apply in man by Hutch & Smith (1969) and Broberger & Aperia (1975).

In the experimental investigations, parameters of renal blood flow and renal function were studied during the application of pressures at different levels within the urinary tract. Consequently, it was possible to judge changes occurring after a long-term reflux with greater certainty. When the changes after free reflux for three months were assessed the contralateral kidney served as a control. It was seen that no compensatory increase in glomerular or tubular function had developed and that the changes in flow and function at increasing intravesical pressure were the same as those observed previously (III). Glomerular function was not significantly changed during anaesthesia alone or when the contralateral ureteric pressure was increased. When the intravesical pressure was elevated, with or without the existence of a unilateral free reflux, the main decrease in the glomerular function of the control kidney occurred at intravesical pressures of 50 and 75 mm Hg. When the pressure in one of the ureters was elevated, a decrease in the glomerular function of the corresponding kidney was already evident at a pressure of 25 mm Hg. The tubular function fell as a rule during every experiment. During neuroleptanaesthesia the decrease was rather small,

whereas during elevation of the intravesical pressure, with or without pre-existing unilateral reflux, the control kidney showed a marked decrease at pressures of 50 and 75 mm Hg, resembling that of the glomerular function. During unilateral elevation of the ureteric pressure, the contralateral tubular function exhibited the same alterations as during neuroleptanaesthesia alone but, in the kidney subjected to elevation of the ureteric pressure, a decrease was already evident at a ureteric pressure of 25 mm Hg.

CLINICAL CONSIDERATIONS

The experimental investigations have shown that the presence of a sterile vesico-ureteric reflux, which appears at a low intravesical pressure, will result in a lowering of glomerular and tubular function in the growing pig. There will also be a reduction in the ability of the corresponding kidney to maintain a steady blood flow when the retrograde pressure is elevated. It is wise to be cautious in extrapolating these experimental findings to the growing child. However, according to preliminary results of a study in progress (Broberger & Aperia, 1975), glomerular and tubular function in children with a grade 3 reflux will decrease with advancing age in children older than five years of age. It remains to be established whether or not glomerular and tubular function normalize after disappearance of the reflux.

To ascertain if operative treatment is indicated earlier than was instigated in patients on chemoprophylaxis for two years without regression of the reflux, repeated clinical studies including split function investigations will be necessary. Further methods of forming an estimate of renal functional changes will also be needed before the experimental results can be fully applied to the growing child.

GENERAL SUMMARY

In a prospective study of 104 children with in all 145 refluxing ureters, the reflux disappeared in 41 patients (53 ureters) within two years from the start of chemoprophylaxis.

During the first year after the discovery of the reflux, 22 children (30 ureters) fulfilled established criteria for early operative treatment. During the second year of chemoprophylaxis, another 12 children (19 ureters) were operated. After two years of chemoprophylaxis, vesico-ureteric reflux remained in 29 children (43 ureters). The reflux was then considered irreversible and the patients operated. Endoscopy including catheterization of the distal ureter proved valuable in the selection of patients for operation. The endoscopic finding of no submucosal tunnel could generally be confirmed at operation. This indicates that there is only a minor risk of overdiagnosing abnormal ureteric orifices at endoscopy.

The postoperative follow-up period was one year. At that time, 90 of 92 reimplanted ureters were free of reflux. One patient was later re-operated due to a postoperative ureteric stricture. When the reflux had disappeared, the frequency of urinary tract infections was considerably diminished.

The occurrence of free reflux at micturition urethrocystography was unrelated to the length of the submucosal ureteric segment. Pyelonephritic changes were more extensive and occurred more frequently in cases with marked reflux on micturition, but seemed not to be influenced by the presence or absence of free reflux.

It was established that pyelonephritic changes seldom appeared or progressed when chemoprophylaxis against infection had been started. As to the prognosis of the reflux it was found that the simultaneous occurrence of free reflux and marked reflux on micturition rendered it less probable that the reflux would disappear spontaneously.

Operation usually caused a temporary dilatation of the upper urinary tract that disappeared during the first month.

The long-term effects of a free and sterile vesico-ureteric reflux on renal blood flow and function were studied experimentally in the growing pig. During three months of free reflux, glomerular and tubular function decreased by about 50 per cent. When exposed to elevation of the retrograde ureteric pressure, renal blood flow oscillated irregularly, which lends support to the supposition that prolonged and sterile, free, vesico-ureteric reflux interferes with the renal circulation.

In comparative studies of renal blood flow and function during neuroleptanaesthesia alone and combined with elevation of the intravesical pressure, it was found that neuroleptanaesthesia alone caused a small decrease in tubular function. When the intravesical pressure was elevated to 50 or 75 mm Hg, a decrease of both glomerular and tubular function was recorded. Renal blood flow did not change during these experiments.

When the retrograde ureteric pressure was elevated without preexisting reflux, a reduction of glomerular and tubular function was already noticeable at a pressure of 25 mm Hg. At greater pressures, the decrease in function was comparable to that observed when the pressure was applied intravesically.

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SONDERDRUCK

Vesico-Ureteric Reflux in Children¹

I. A Therapeutical Approach and a Prospective Study

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According to BETTEX (1967) and HUTCH et al. (1972) vesico-ureteric reflux (VUR) may be classified as of congenital origin (primary VUR) or acquired (secondary VUR). As suggested by several authors (6, 13, 20, 25, 53) congenital anomalies causing primary reflux are ectopic ureters and ureterocele, ureteral duplication and bladder diverticuli. STEPHENS (1963) also focused interest upon the abnormally high cranio-laterally situated ureteral orifice with poor connection to the trigone viz. the *dysto-*

pic ureter as being a congenital anomaly causing VUR.

The acquired VUR may be secondary to infravesical obstruction, neurogenic bladder disease or lesion, operative trauma to the distal ureter or secondary to intravesical inflammatory reactions.

To distinguish between primary and secondary VUR is of utmost therapeutic importance. Secondary VUR due to inflammatory reactions may be reversible, provided the urinary tract infection (UTI) is successfully treated with chemotherapy and prevented by long-term chemoprophyl-

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laxis (8, 20). Primary VUR, on the other hand is considered irreversible, requiring surgical correction.

Information gained by endoscopy and ureteral catheterization may be diagnostic in differentiating between primary and secondary VUR. However, in children with VUR, the question often remains open whether the origin of the VUR is congenital or acquired as a result of endoscopic examination, however carefully performed. During such conditions it is necessary to find other guiding principles.

This report renders an account of a therapeutical approach and a prospective study in the treatment of VUR in children. One of the main aims was to try to outline a procedure of differentiation by exclusion between primary VUR and VUR secondary to UTI.

Material

The series included 104 children, 78 girls and 26 boys, with VUR in 145 ureters. The right ureter was affected in 25 children and the left one in 36, while in 42 children the VUR was bilateral. Table I shows the reasons for admittance. 72 children were

Table I Reasons for admittance in 104 children with VUR

Recurrent UTI : s	68
One UTI before 6 months of age	11
One UTI after 6 months of age	9
Recurrent asymptomatic bacteriuria	4
Enuresis	7
Misc. (albuminuria, haematuria etc.)	5
	104

Table II Onset of symptoms

Age in years	No of patients	
0—1	35	} 85 (82 per cent)
1—2	11	
2—3	20	
3—4	19	
4—5	7	
5—6	5	
6—7	2	
7—	5	
	104	

referred because of recurrent UTI's. 20 revealed a history of only one attack of acute pyelonephritis. The remaining number included a few cases of enuresis (7 children) and albuminuria, haematuria and minor urologic complaints (5 children). Secondary VUR in connection with lower urinary tract obstruction, iatrogenic damage and neurogenic bladder disease were excluded.

The onset of symptoms appeared before four years of age in 85 children (Table II).

Diagnostic Procedures and Criteria in UTI

Urine for bacteriologic and microscopic examination was taken as clean voided specimen, cooled and transported to the laboratory as described by BERGSTRÖM et al. (1972). Diagnostic criteria included a bacterial count of 100,000 microorganisms or more per millilitre of urine.

Therapeutical Approach

Differentiation of reflux into primary and secondary, itself represents

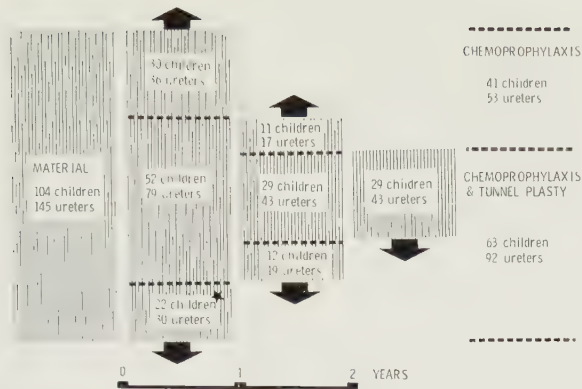


Fig. 1 Survey over material and results. Time axis below. Upward arrows indicate VUR disappeared on chemoprophylaxis only. Downward arrows indicate VUR surgically treated

* Including 1 patient (2 ureters) who got UTI in spite of chemoprophylaxis

a step towards a guiding therapeutical principle. Primary VUR remains in spite of adequate chemoprophylaxis as the origin is anatomical. Secondary VUR on the other hand may disappear after successful treatment of the UTI provided the inflammatory tissue reactions are reversible. Beyond these pathogenic conditions the actual morphological changes of the kidney and the urinary tract have also to be considered.

In consequence our therapeutical approach was based upon an effort of early differentiation into primary and secondary VUR's by the aid of endoscopy followed by operative treatment of primary VUR's and prolonged chemoprophylaxis of secondary VUR's. Two weeks' absence of UTI was also considered a prerequisite for operative treatment. In many instances, however, a clear-cut reliable differentiation could not possibly be obtained. On those occasions long term

chemoprophylaxis was chosen as a means of attempting differentiation.

Basic Investigations

Reflux was diagnosed and classified by means of standardized *micturition urethrocystography* (MUC) into free reflux and reflux and micturition. Special care was devoted to evaluate the dilatation of the ureter and renal pelvis. Renal size and kidney scarring were minutely judged on *urography*. The results of the roentgenological examinations are reported separately (37).

On *endoscopy* the ureteral orifices were examined with regard to their shape, size and peristaltic activity as well as their mutual position and position within the trigone. *Catheterization* of the distal ureter was performed to evaluate the length and course of the intravesical ureter. A catheter number 3 French with a slightly bent tip proved favourab-

le. For evaluation of *the renal function*, the concentrating ability as well as blood-urea-nitrogen or creatinine were measured. Impairment of function was in addition assessed by isotopic renography and creatinine clearance. Following these examinations a decision was made between operation or long-term chemoprophylaxis.

Indications for Early Operative Treatment

1. Ectopic ureter with reflux.
2. Free reflux into a tortuous, profoundly dilated ureter and the endoscopic findings of an abnormal position or course of the distal ureter in children older than three years of age.
3. Ureteral orifice opening into the bottom of a diverticulum.
4. Agenesis of one kidney and free reflux into the contralateral dilated ureter und pelvis.
5. Bilateral reflux into dilated ureters and pelves in connection with impaired renal function and/or advanced renal scarring.

Long term Chemoprophylaxis

Prophylaxis against UTI was given to the remaining patients. Nitrofurantoin (Furadantin®, Pharmacia, Sweden) in a dose of 3 milligrams per kilogram bodyweight and day divided into 2 doses was primarily used. The prophylaxis was given daily for up to two years to keep the child free of UTI provided the reflux or dilatation of the upper urinary tract did not progress.

Urine examinations in the related way were undertaken monthly. MUC was undertaken every six months.

Operative Procedure

Ureteroneocystostomy according to the technique described by POLITANO-LEADBETTER (1958) was used with the exception that the distal 1 — 2 cm of the ureters were resected. A tunnel plasty was created to a length of 2 — 2.5 cm. Particular attention was paid to attaching the ureter carefully to the trigone and to obtaining close contact at the anastomosis between the bladder mucosa and the ureter using chromic catgut 6/0. Indwelling ureteric catheters were used only in duplicated ureters. Suprapubic bladder drainage was carried out for 3 — 4 days postoperatively.

Postoperative Therapy and Follow-Up

The children were given intravenous fluid and electrolytes the first postoperative day and ampicillin (Doktacillin®, Astra, Sweden) 100 milligrams per kilogram bodyweight for 3 — 5 days. Prophylaxis with nitrofurantoin was then maintained for 6 months.

The roentgenologic controls included urography one week, one month and twelve months, and MUC six and twelve months postoperatively. When ureteral dilatation was revealed on the one-month-urography another check up was undertaken two

months later (37). Urine examinations were undertaken monthly.

Outcome of the Therapeutical Approach (Figure 1)

Early operations:

Twentyone patients with in all 28 refluxing ureters were operated according to the indications mentioned previously:

Two patients (3 ureters) had free reflux into dilated ureters with abnormal appearance of the orifice ("golf-hole-orifice"). In 9 patients (13 ureters) free reflux into profoundly dilated ureters with a perpendicular course and abnormal position of the orifice was diagnosed. In 3 patients (3 ureters) the ureters opened into the bottom of a diverticulum. Agenesis of one kidney combined with reflux into a dilated ureter was demonstrated in one patient and pronounced pyelonephritic scarring with reflux into dilated ureters and pelvis in 6 patients (8 ureters). Two of these (3 ureters) had impaired renal function.

In addition one patient (2 ureters), who got recurrent UTI's in spite of chemoprophylaxis was also operated.

Long term chemoprophylaxis

A total of 82 remaining patients with 115 refluxing ureters were given prophylaxis against UTI for 6 — 24 months. The results are reproduced in fig. 1. Within 6 month's prophylaxis 13 patients (15 ureters) were free of reflux. During the following 6 months the reflux disappeared in another 17

children (21 ureters) and between 12 and 24 months after the start of chemoprophylaxis another 11 patients (17 ureters) demonstrated normal MUC's. Thus in all together 41 patients (53 ureters) the VUR disappeared on chemoprophylaxis only.

Operation after more than one year of chemoprophylaxis:

Twelve patients with, in all, 19 refluxing ureters were operated before the ending of the scheduled two years of chemoprophylaxis for the following reasons: Unchanged or progressive dilatation of the upper urinary tract in 6 patients (9 ureters), impaired renal function (1 patient, 2 ureters) and late confirmed anomalies (1 patient with bilateral diverticuli and reflux and 1 patient with a ureterocele and bilateral free reflux). In addition 3 children with 4 ureters refluxing into bifid systems were also operated.

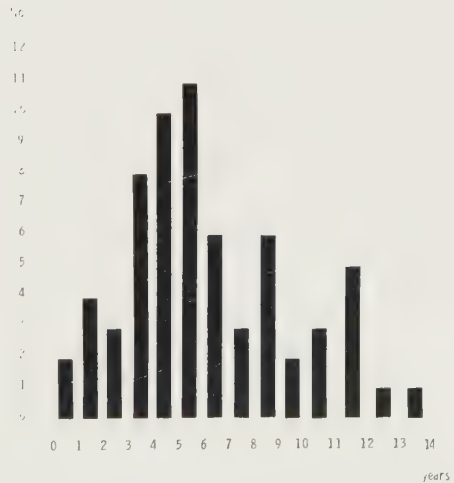


Fig. 2 Age at operation in 63 children with VUR

The remaining 29 patients with reflux into 43 ureters were operated after two years or more of chemoprophylaxis as it was considered that as chemoprophylaxis had prevented UTI for such a long time, the reflux would have been caused by anatomical abnormalities. In these cases the indications for surgical intervention were accordingly outlined by means of differentiation by exclusion.

The age of all children at operation is reproduced in figure 2.

Endoscopic Judgements

Endoscopy was carried out in 55 of the 63 operated patients. The intravesical part of 81 refluxing ureters was assessed by inspection and catheterization. The length of the intravesical ureter was stated as normal, short or absent. An intravesical length of at least 0.3 centimetres in a newborn, 0.5 centimetres in a one year old child and 0.8 centimetres in children up to ten years of age was regarded as normal. Endoscopic and operative findings regarding the length of the intravesical ureter could be correlated in 65 ureters.

Table III shows that 24 ureters were found on endoscopy to have no demonstrable intravesical part and this was verified at operation. Of 24 ureters with endoscopy revealing a short intravesical part, 17 were also found short at operation, whereas 7 had no visible intravesical part whatsoever. Of 17 ureters stated on endoscopy to have a normal intravesical part, 7 were at operation found to

Table III Endoscopic and operative judgement of the intravesical ureteric part in operated patients with VUR

Intravesical ureter at endoscopy	No of refluxing ureters	Intravesical ureter at operation
Absent	24	Absent — 24 * Short — 0 Normal — 0
Short	24	Absent — 7 Short — 17 Normal — 0
Normal	17	Absent — 7 Short — 3 Normal — 7
	65	

* Including 3 diverticuli

Table IV Endoscopic judgement of the intravesical ureteric part in not operated patients with VUR

Intravesical ureter at endoscopy	No of refluxing ureters
Absent	1
Short	7
Normal	40
	48

have no tunnel, whereas 3 had short ones.

In the group of 41 children where the VUR disappeared on chemoprophylaxis only, 48 of the 53 refluxing ureters were judged on endoscopy. 40 were stated as having a normal intravesical part and 7 as having a short one. One ureter had no visible intravesical part (Table IV).

Efficiency of Chemoprophylaxis

In 92 of 104 patients with VUR nitrofurantoin was proved effective

Table V Chemotherapeutics used for prophylaxis against UTI

	No of patients
Nitrofurantoin	92
Sulphonamide	24 *
Nalidixic acid	4
Ampicillin	2

* 18 before admittance

in keeping the urine sterile (Table V). If UTI was due to bacteria resistant to nitrofurantoin and where gastrointestinal side effects appeared during the treatment other drugs were administered.

Operative Results

MUC 12 months after operation revealed that 90 out of 92 reimplanted ureters were free of reflux, a cure rate of 98 per cent. The postoperative roentgenological findings are described elsewhere (37).

Complications

In one child urography after one year revealed reduced but persistent dilatation in one of the operated ureters. Endoscopy disclosed distal ureteric stricture. The child was later reoperated successfully. In 6 other instances urography one month post-operatively demonstrated some dilatation, but at later controls it had disappeared without specific measures except in one patient known to have a slight ureteric stricture.

Postoperative UTI

Four out of the 63 operated children developed UTI during the fol-

low-up period. Of 27 patients in whom reflux disappeared on chemoprophylaxis only and later followed at our outward unit for six months, four got UTI.

Discussion

The relationship between VUR and UTI has been thoroughly discussed. CAMPBELL (1951) found a VUR rate of 12 per cent, KJELLBERG et al. (1957) 34 per cent, GROSS et al. (1961) 47 per cent. According to HUTCH (1962) it is possible to point out VUR in about 50 per cent of all children with UTI's. Our material constitutes a selection from an area comprising about 1.8 million inhabitants. The children have been admitted after a different number of UTI's according to differing local policy. This kind of selection, of course, excludes every possibility of reaching a conclusion about the incidence of UTI and VUR within the population.

VUR is nowadays regarded as abnormal at all ages including newborns (22, 31, 33, 40). However, the reverse opinion has earlier been claimed by different authors. GIBSON (1949) reported 2 infants with VUR among 43 children up to 12 years without urological complaints. They were, however, not endoscoped and consequently the VUR's could have been primary. IANNACCONE et al. (1955) found VUR in 1 out of 50 cystographed infants. They also did not perform endoscopy. With silver iodide and thorium nitrate as contrast media KRETSCHMER (1916) produced

VUR in 3 out of 10 examined children. KÖLLERMANN et al. (1967) considered VUR a normal phenomenon in infants and children up to three years. He produced VUR in 65 per cent of infants by extensive filling of the bladder with contrast medium. Accordingly many of these examinations revealing VUR as a normally existing phenomenon seem to be carried out in an incomplete or unphysiological way.

Our material was limited to comprise primary VUR and VUR secondary to non-obstructive UTI only. VUR secondary to lower urinary tract obstruction, iatrogenic damage and neurogenic bladder disease were excluded. These conditions usually reveal multifocal findings and their treatment must be directed towards the basic disease. This type of secondary reflux does not constitute a diagnostic-therapeutical problem similar in character to primary VUR.

The series described consisted of 78 girls and 26 boys, corresponding to the sex-relationship of 3 to 1. Similar distribution has also been reported (1, 2, 12, 41) and may probably reflect the higher incidence of UTI in girls (10, 17, 23). There is, however, a male preponderance among UTI in newborns (5, 38) probably due to the male's greater susceptibility to infections of all types in this age-group (36, 51).

The probability of incompetence at the uretero-vesical junction is, due to a shorter tunnel, greater in infancy than in older age groups (20). This

was substantiated in our material by the fact that 82 per cent of the children fell ill before 4 years of age. Corresponding figures have also been reported (15,47,53).

There was approximately equal distribution between left and right sided reflux in our material. A certain dominance of bilateral VUR existed (40 per cent) corresponding to previous findings (12, 25) but predominance of unilateral VUR has also been reported (26). Nor did we find any clear-cut difference with respect to the sides in the group with reflux between those on chemoprophylaxis only and those operated. This observation speaks in favour of no differences in side-distribution between VUR of primary origin and VUR secondary to UTI.

Specific symptoms of VUR are lacking. Recurrent UTI's or flank pains on micturition sometimes indicate VUR. Recurrent asymptomatic bacteriuria exists in a comparatively high frequency in girls, about 1.1 per cent (29). It has also been noticed that elderly patients with chronic non-obstructive pyelonephritis had had UTI and VUR in early childhood and probably also, during long periods, clinically silent UTI's (18, 36). Accordingly it is in our opinion of great importance that a thorough roentgenological examination of children suffering from recurrent asymptomatic bacteriuria is performed. This policy resulted in early diagnosis in four patients in our material.

The preoperative judgement was mainly based upon MUC (37) and endoscopy. The endoscopic diagnosis of abnormal ureterovesical junctions showed throughout good correlation to the findings at operation. However of 17 ureters stated on endoscopy to have a normal intravesical part, 7 were at operation found to have no tunnels whereas 3 had short ones. This indicates that there is a minor risk of overdiagnosing abnormal ureteric orifices on endoscopy. Out of 58 ureteric orifices found to be abnormal at operation 48 had already at endoscopy been judged abnormal with little chance of recovering from reflux without operative correction. Consequently, in our opinion, endoscopy has proved to be a valuable tool in the selection of patients for early operative treatment.

In 41 children the VUR disappeared on chemoprophylaxis against UTI. The endoscopic assessment of the intravesical ureters could therefore not be correlated to the findings in the open bladder. From that point of view it is not possible to make any *definite* conclusions regarding the value of endoscopy. However, the results have shown that endoscopy offered a *certain* basis for evaluation and selection of patients to operation or long-term chemoprophylaxis respectively.

The indications used for early operative treatment in this investigation coincide mainly with current practice:

Ectopic ureters with VUR posses

no anatomical prospects of normalizing spontaneously (8, 20). The *dys-topic position* on the other hand may be corrected by growth, provided the ureterovesical junction is allowed time to grow without complicating infections. Thus, in doubtful cases with subnormal length of the submucosal tunnel, especially in children under three years of age, chemoprophylaxis against UTI was chosen in preference to operation.

Bladder diverticuli on the other hand, with a ureter opening into the bottom of the diverticulum give no alternative. It has been accepted long ago that the normal valve mechanism is lacking, necessitating operative correction (49).

In addition to the above mentioned indications, early operative treatment was also preferred in the following conditions and for the following reasons:

Unilateral renal agenesis combined with *free reflux into the dilated contralateral ureter and pelvis*: These conditions mean a potential risk for extensive renal damage in case of infection. The operative treatment was chosen to ensure protection of the solitary kidney.

Severely impaired renal function: BETTEX (1965) and KUFFER et al. (1968) urged the avoidance of operative treatment due to the risk of effluent blocking and increasing renal insufficiency. In our opinion, it may be justified to perform bilateral operative correction in a two step procedure otherwise the destructive process

will continue and hopes of recovery diminish. This argumentation was applied in two patients resulting in a certain improvement. However, in one of them a small reflux into one of the ureters remained postoperatively.

The majority of the children did not fulfil the requirements of the indications for early operative treatment. They were consequently all given long-term chemoprophylaxis for the scheduled two-year period. During this time a certain number of them had to be operated. The decisions to operate were based upon the results of repeated investigations.

At the end of the two-year period of chemoprophylaxis 29 of the 104 children still had reflux. They were all free from UTI and a considerable time had been allowed for healing of the secondary tissue changes causing reflux which had been presumed reversible. On that basis the VUR's were classified as irreversible and the patient operated.

The result of our therapeutical approach justifies in many respects our policy. On the other hand this approach, no doubt, exposed some children to a considerable number of MUC's involving increased radiation dose especially to the gonads and induction of UTI prior to the decision to operate.

However, the radiation effects were reduced to a minimum using only a few exposures per investigation (37) and infections secondary to the catheterization could be avoided through

minute sterility. Nevertheless, in our opinion, the conclusion must still be open whether or not it is necessary to wait for operation two years or less when diagnosis is not confirmed anatomically.

Nitrofurantoin was used predominantly for the prevention of UTI. Many publications have shown its efficiency in the prophylaxis against UTI in children (9, 39 and others). Recurrence of UTI during prophylaxis was rare and resulted in a temporary change in medication usually to sulphonamide. In only a few cases did side effects of nitrofurantoin, such as vomiting and loss of appetite, cause a change to other drugs. An important advantage in nitrofurantoin over sulphonamide for prophylaxis is that no ecologic effects on the intestinal flora appear (34).

Recurrent UTI was the predominating reason for bringing the children with VUR to examination and diagnosis. When the VUR had disappeared the frequency of UTI's to a large extent decreased. Only 6 per cent of the children operated on and 15 per cent of the nonoperative group developed UTI during a six months period after the prophylaxis had been withdrawn. These figures speak in favour of the supposition that VUR not only can arise as a consequence of UTI, but can also be a contributing factor in the genesis of recurrent UTI's. However, as pointed out by BERGSTRÖM et al. (1968), one has to be cautious before classifying a patient with UTI as cured.

According to SCOTT (1969) recurrent UTI's in children with VUR disappear in 75 per cent of the successfully operated patients, but different results have been reported (52 and others).

The most important effect of successful treatment of VUR is probably a considerable reduction in the number of recurrent pyelonephritis cases. SCOTT et al. (1968) found pyelonephritic scarring to be more than eight times more common in children with UTI *and* VUR than in children with UTI *without* VUR.

Many children with VUR form residual urine. This means a greater risk for recurrent UTI's (48), and thus constitutes a reason for wide indications for chemoprophylaxis.

Regarding the hydrodynamic effect of VUR on renal growth and function published reports are not consistent. ASANO (1970) has shown delayed excretion in VUR when the bladder acts as a reservoir as measured on isotopic renogram. It has also been suggested (24, 32, 50) that VUR without infection is harmless to the kidney.

Renal atrophy has been shown to be the result of persisting VUR even without infection (44). With increasing ureteric dilatation peristalsis is reduced (45, 49), but peristaltic activity has been demonstrated even in markedly dilated ureters (43).

The results of this study including two cases with persisting reflux and one operative complication among 145 refluxing ureters indicate that

the approach applied has effectively reduced the number with reflux and accordingly eliminated the conditions for recurrent ascending pyelonephritis. The information gained by a carefully performed endoscopy, including catheterization of the terminal ureteric course proved valuable in the differentiation between primary and secondary VUR. However, further judgement of the results of the approach demands long-term follow up of the patients.

Summary

In a prospective study of 104 children with in all 145 refluxing ureters, the reflux disappeared in 41 patients (53 ureters) within two years of chemoprophylaxis.

During the first year after the discovery of the reflux 22 children (30 ureters) fulfilled established criteria for early operative treatment. During the second year of chemoprophylaxis another 12 children (19 ureters) were operated.

After two years of chemoprophylaxis vesico-ureteric reflux still remained in 41 children (62 ureters). They were all operated. The endoscopic judgement of the position of the ureteric orifice and the length and course of the submucosal tunnel showed a good correlation to the findings at operation. This indicates that there is a minor risk of overdiagnosing abnormal ureteric orifices on endoscopy.

After a postoperative follow up period of one year only two patients still had vesico-ureteric reflux. In one patient a postoperative stricture at the vesico-ureteric junction caused reoperation. The frequency of urinary tract infections was considerably diminished after the cessation of the reflux.

Zusammenfassung

Bei einer prospektiven Studie an 104 Kindern mit insgesamt 145 Refluxureteren verschwand der Reflux bei 41 Patienten (53

Ureteren) unter Chemotherapie innerhalb von 2 Jahren.

Während des ersten Jahres nach Erkennung des Refluxes konnten bei 22 Kindern (30 Ureteren) die Kriterien für eine frühe operative Behandlung festgestellt werden. Während des zweiten Jahres der Chemotherapie wurden weitere 12 Kinder (19 Ureteren) operiert.

Nach 2 Jahren Chemotherapie blieb bei 41 Kindern (62 Ureteren) ein vesiko-ureteraler Reflux weiterhin bestehen. Sie wurden alle operiert.

Die endoskopische Beurteilung des Sitzes des Ureterostiums, der Länge und der Verlaufsrichtung des submukösen Tunnels wurde bei der Operation bestätigt. Das zeigt, daß nur ein geringes Risiko besteht, eine anomale Ureterenumündung bei der Endoskopie überzubewerten.

Postoperativ bestand nach 1 Jahr nur noch bei 2 Patienten ein vesiko-ureteraler Reflux. Bei einem Patienten machte eine postoperative Strikture im Bereich der vesiko-ureteralen Verbindung eine Nachoperation erforderlich.

Die Häufigkeit der Harnwegsinfektionen war nach Behebung des Refluxes beträchtlich verringert.

Résumé

Au cours d'une étude prospective de 104 enfants avec en tout 145 reflux vésico-urétéraux, le reflux disparut chez 41 patients (53 uretères) sous l'effet de la chimiothérapie dans le délai de 2 ans.

Pendant la première année qui suivit la découverte du reflux, les critères pour un traitement chirurgical précoce purent être établis chez 22 enfants (30 uretères).

Pendant la 2^e année de la chimiothérapie il fallut opérer encore 12 enfants (19 uretères).

Après 2 ans de chimiothérapie, il resta 41 enfants (62 uretères) porteurs de reflux vésico-urétéral. Tous furent opérés.

La signification du siège de l'ostium urétéral fut établie par endoscopie, de même que le parcours du tunnel sous muqueux, précisé au cours de l'opération. Cela montre qu'il n'y a qu'un risque très faible de méconnaître par endoscopie une anomalie orificielle de l'uretère.

A titre post-opératoire, après un an, le reflux ne persistait plus que chez 2 patients. Une sténose post-opératoire survint chez un autre au niveau de l'anastomose vésico-urétérale rendant une reprise chirurgicale nécessaire.

La fréquence de l'infection urinaire fut considérablement réduite après traitement du reflux. *Pré*

Resumen

En un estudio prospectivo en 104 pacientes con 145 reflujo, en 41 pacientes (53 ureteres) desapareció el reflujo con antibioterapia en el plazo de dos años.

En el primer año de antibioterapia, hubo que operar en los restantes enfermos a 22 niños (30 ureteres). En el segundo año se operaron 12 pacientes (19 ureteres).

Después de los dos primeros años de antibioterapia en 41 niños (62 ureteres) no se alteró su reflujo vesicoureteral. Todos hubieron de ser operados. La valoración endoscópica de la posición del ostium ureteral, su trayectoria y longitud, fueron confirmados en la intervención. Por otro, lado la desembocadura anómala de ureter es tan rara, que la endoscopia alcanza un enorme valor diagnóstico.

Postoperatoriamente solo en dos enfermos quedó un reflujo vesicoureteral. En un paciente apareció una estenosis postoperatoria, en la zona de la unión vesicoureteral. Con el tratamiento indicado y la desaparición del reflujo quedó la frecuencia de la infección urinaria enormemente disminuida. *Boi*

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SONDERDRUCK

Vesico-Ureteric Reflux in Children¹

II. Roentgenologic Examination

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This article reports the results of roentgen examinations in children with vesico-ureteric reflux (VUR) described by HELIN et al. (7).

Material

The patients were divided into two groups according to treatment: Group A consists of children operated upon with ureteroneocystostomy and group B of children who were not operated upon.

No patient had ureterocele, neurogenic bladder disease or urethral obstruction. One patient in group A had a 5-cm-long inflammatory stricture distally in one of the ureters with reflux (verified by microscopy).

Group A

This group includes 63 children with 92 refluxing ureters operated because of VUR. As 3 of the patients had only one kidney (unilateral agenesis or nephrectomy having been performed earlier) and one had a complete duplication of pelvis and ureter unilaterally, the total number of kidneys and ureters examined was 124.

In two children operated unilaterally, the reflux was initially bilateral, but disappeared on one side during the pre-operative medication. These two kidneys and corresponding ureters with reflux healed on chemoprophylaxis and are also dealt with in group B.

The number of roentgen examinations performed — micturition urethrocytography and urography — is given in table I. The time lapse from the first roentgen examination to the operation varied from 1 to 76 months (mean 22, S. D. 18 months) and the postoperative follow-up period from 12 to 38 months (mean 16, S. D. 6 months).

Group B

This group includes 41 children with reflux into 53 ureters who became free of VUR on chemoprophylaxis before an appointed time. Two of them, who had anti-reflux operation performed on one side, are, concerning the operated side, included in group A.

One patient had a complete duplication of the pelvis and ureter on one side. Totally 81 kidneys and ureters were examined. The number of roent-

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gen examinations performed is given in table I. The time lapse between the first and latest examination varied from 1 to 116 months (mean 22, S. D. 19 months).

Methods

Urography was performed using conventional methods.

At micturition urethrocystography (MUC) a 20 per cent iodine contrast medium was allowed to drip slowly into the bladder. At the primary examination a complete investigation was made of the anatomy of the bladder and the urethra and of the occurrence of VUR. Five exposures were made as follows:

1. Before the first exposure the bladder was filled with contrast medium until the intravesical pressure came into equilibrium with a pressure of 25 cm H₂O. This exposure — an abdominal survey — was made to demonstrate possible occurrence of free reflux.

2. Before the second exposure, the bladder was filled with additional contrast medium until the patient felt the urge to urinate. During forced micturition one exposure was made in lateral position.

3. A third exposure was made in supine position during forced micturition, with the central beam parallel to the pelvic floor.

4. A fourth exposure was made in supine position as an abdominal survey during forced micturition.

5. Another exposure was made as an abdominal survey immediately after the micturition was finished, to demonstrate any reflux at the moment voiding was completed.

Some of the examinations were performed at other hospitals with varying examination techniques.

At the check examinations, only VUR was tested. To reduce the gonad dose only three exposures were made, namely numbers 1, 4 and 5. Conven-

Table I The number of urographies (URO) and micturition urethrocystographies (MUC) performed on patients in groups A and B

Number of Examinations	Number of patients					
	Group A			Group B		
	Preoperative MUC	URO	Postoperative MUC	URO	MUC	URO
1	13	27	6		15	
2	23	19	50	7	19	16
3	17	10	6	34	6	13
4	8	5	1	17	1	12
5	2	2		4		
7				1*		

* Complicated by development of ureteric stenoses explaining the many examinations

tional technique with intensifying screen and full-size film was used, but no fluoroscopy.

The gonads of the boys were protected at urography with a lead cover and also at MUC when possible (exposures numbers 1 and 5). In girls the contrast-filled bladder affords a certain exposure protection to the gonads at antero-posterior beam direction. The gonad dose to boys was about 600 mRad at the primary and 275 mRad at the check examination.

Statistical methods

Mean values and standard deviations (S. D.) were calculated for a number of groups. Quantitative differences were judged by conventional t-tests.

Interpretation and definitions

Destruction or deformation of a papilla, scarring or general reduction of the renal parenchyma were interpreted as pyelonephritic changes. The degree of the parenchymal changes was expressed as a renal size index: the long axis of the kidney was expressed in per cent of the distance from the upper border of the first lumbar vertebra, to the lower border of the fourth. The index was not determined in the following cases: if the kidney could not be delineated clearly, if it had a double pelvis, or if it was a "single kidney".

If the ureters from a kidney with two pelvises fused and thus had a common orifice, the ureters were classified as one ureter. When there was a complete duplication of the ureter and pel-

vis, not only the ureters were counted as two, but also the kidney.

The width of the pelvis and ureters was evaluated from the urographic examination *without* abdominal compression.

Reflux grade 1 means that the contrast medium goes up into the ureter but does not reach the pelvis. At reflux grade 2 the pelvis is also filled and grade 3 means that there is also a distension of varying degree of the upper urinary tract. Distension in this context means that the upper urinary tract is wider than at urography without abdominal compression. Reflux means reflux during micturition. Reflux before micturition is called free reflux.

Results

Group A. Preoperative examinations

The results of MUC are given in table II.

In those cases in which MUC was performed more than once, the degree of reflux was unchanged except in two cases: in one case it increased and in another it decreased somewhat.

Table II Degree of reflux at last pre-operative micturition urethrocystography in 63 children (corresponding to 124 ureters), who later underwent anti-reflux operation

	Number of Ureters	
	Total	Operated
No reflux	29	
Reflux Grade 1	2	1
Reflux Grade 2	32	31
Reflux Grade 3	61	60
n =	124	92

Examination in order to study the occurrence of free reflux was made in 65 of the ureters later operated. Free reflux was found in 56 (86 per cent).

When both free reflux and reflux on micturition occurred there were pyelonephritic changes in 45 per cent in the corresponding kidney. In kidneys belonging to ureters with reflux only at micturition, there were pyelonephritic changes in 38 per cent.

Parenchymal changes were very common in kidneys with marked micturition reflux (table III). The renal size index also decreased parallel to the increase of the degree of reflux (table IV). The difference in the index between the group without reflux and that with reflux grade 3 was significant ($p < 0.01$).

A comparison between the length of the submucosal ureteric segment and, respectively, the occurrence and degree of free reflux and reflux on micturition, is given in table V. Irrespective of the length of the submucosal segment of the

Table III The frequency of renal parenchymal changes at varying degrees of reflux at micturition registered at the first MUC

n = number of kidneys

	No Reflux	Reflux Grade 2	Reflux Grade 3
Group A	10 %	25 %	72 %
n =	29	32	61
Group B	3 %	13 %	80 %
n =	28	40	5

Note: Reflux Grade 1 occurred into 2 ureters in group A and into 8 ureters in Group B. There were in no case parenchymal changes in the corresponding kidneys

Table IV Relation between renal size index and degree of reflux. In group A figures refer to last pre-operative examination and in group B to last examination. n = number of kidneys. (For technical reasons it was not possible to calculate the index in all cases.)

	Group A		Group B	
	mean	SD	n	n
No reflux	98	12	26	97
Reflux Grade 1				95
Reflux Grade 2	94	10	22	98
Reflux Grade 3	90	11	41	88

Table V Relation between the length of submucosal ureteric segment in 73 ureters, determined at operation, and the degree of reflux before and during micturition. The possibility of occurrence of free reflux was investigated in only 56 of the ureters. The percentage distribution is given in brackets

	Number of Ureters Length of submucosal ureteric segment		
	Normal	Short	Absent
Free reflux:			
None	1 (17)	2 (14)	5 (14)
Grade 1			1 (3)
Grade 2	3 (50)	4 (28)	9 (25)
Grade 3	2 (33)	8 (57)	21 (58)
n =	6	14	36 = 56
Mict. reflux:			
Grade 1	1 (17)		
Grade 2	3 (50)	11 (50)	6 (13)
Grade 3	2 (33)	11 (50)	39 (87)
n =	6	22	45 = 73

ureters, if absent, short or of normal length, the frequency of free reflux was the same. The degree of reflux, both free and on micturition, however, showed a trend to be less marked if the submucosal segment was of normal length.

In all cases except one, the pyelonephritic changes, if any, were present at the first urography and in four cases they progressed during the preoperative observation period.

Postoperative roentgen examinations were performed according to table I.

On the operated side, reflux occurred after 3 of the 92 ureteroneocystostomies:

1. In one case there was reflux grade 2 six months after the operation but no reflux 6 months later.
2. In one case there was free reflux grade 1 at check examination 12 months after the operation, but no reflux at micturition. Only one MUC was made postoperatively.
3. In one case there was reflux grade 2 at MUC 6 as well as 12 months postoperatively. The reflux was less marked than before operation, however.

In 2 of 3 cases with bilateral reflux but operated on one side only, the reflux disappeared spontaneously on the non-operated side after the other side was operated. The reflux on the non-operated side had been of grade 1 and 2, respectively. (In the third case the reflux was of grade 3.)

During the postoperative check period, reflux grade 2 appeared on the non-operated side in one patient. It had disappeared at the following examination.

In no case did pyelonephritic changes appear in the preoperatively normal kidneys. In 2 cases, however, scarring of the renal parenchyma, which had started preoperatively, progressed after the operation.

At urography performed about one week after the operation, the pelvis and the ureter on the operated side were usually dilated. In a few cases there was also a slight dilatation on the non-operated side. The dilatation had usually disappeared at the examination 1 month after the operation. In 2 cases, however, there was still some degree of dilatation of the upper urinary tract 1 year after the operation. The excretion of contrast medium was not visibly reduced, not even in cases with marked dilatation of the pelvis.

Group B

The frequency and degree of reflux and its relation to pyelonephritic changes in the corresponding kidneys are given in table III and in relation to renal size index in table IV.

In 4 kidneys pyelonephritic changes appeared during the observation period. In the other 7 kidneys with pyelonephritis, the parenchymal changes were present at the first examination and did not change during the observation period.

There was free reflux of grade 2 or 3 in 7 of 30 cases (23 per cent). Only one of the corresponding kidneys showed pyelonephritic changes.

Discussion

Children with urinary tract infections, are often objects of repeated roentgen examinations. Therefore it is a *sine qua non* that the technique used at MUC renders low radiation doses to the gonads. The doses we measured in boys are considerably lower or equal to

most published reports (for references see 5, 12), but lower doses at fluorography are also reported (11). We have not checked the radiation doses to the gonads in girls, but they may be assumed to be higher than in boys. We use a conventional technique with full-size films because this gives a picture which still is much richer in information than that received at present from fluorography and the format is more suitable for covering the total area of interest at MUC.

There is seldom reason to take series of pictures. The risk that a possible reflux will be missed at the check examination when only 3 exposures are made, is very small according to preliminary results of a study in progress (16). Nor have we found that other information of relevance is lost because of excluding the lateral projection at the check examination.

The children in group B were checked with MUC until the reflux disappeared. Further checks were made in only a few cases during the time fixed for this study. There was no follow-up period corresponding to the postoperative observation period in group A. The frequency of re-occurrence has thus not been studied.

It should be stressed that the period of preoperative chemoprophylaxis varied because some cases presented special conditions which were considered to indicate early operation (7).

There is some controversy as to the evaluation of the parenchymal changes. It has been discussed whether they are caused by pyelonephritis only or to any

extent by other conditions such as the hydrodynamic effect of the reflux on the renal parenchyma or of morphological congenital abnormalities. It is also questionable to what extent such hypothetical conditions may pave the way for pyelonephritis. (For survey of these items see 2, 8, 15.) Pyelonephritic changes are practically always found at microscopy in these cases. Therefore we have not tried to make a differential diagnosis. In some cases, however, the parenchymal changes may in reality, to some degree, consist of non-pyelonephritic changes. On the other hand, however, it must be borne in mind that the diagnosis of pyelonephritis at urography is based upon the occurrence of macroscopic changes. Microscopic examination of biopsies from children with normal urography but with proved upper urinary tract infection, has demonstrated pyelonephritis in a very high per cent of the cases in contrast to children with infection localized to the lower urinary tract only (21).

In this study, the parenchymal changes were in most cases characterized by destruction or deformation of usually one or a few single renal papillae and scars in the adjoining cortex, areas of local hypertrophy of undamaged tissue, and asymmetric involvement of the kidneys.

There was a higher frequency of parenchymal changes among kidneys with marked reflux as compared to those with moderate or no reflux. The changes were also more extensive, reflected in the lower renal size index at increasing grade of reflux. In group A this

was in fact more marked than is to be seen in table IV because the mean "age" of the kidneys with reflux grade 3 was lower than that of kidneys without reflux (5.6 and 8.1 years, respectively). Normally the renal size index is somewhat above 100 in infants and small children and somewhat below in children older than 6 (6). Correction for this age variation of the index was not made. The renal size, however, is not dependent on pyelonephritic tissue damage only. The infection per se has a temporary growth-preventing effect on the kidney (1, 10).

In the present study there were 9 kidneys with competent ureteric orifices proved at repeated MUC with pyelonephritic changes and/or renal size index below 90. It is known that there had been VUR earlier in 3 of these cases (2 of these had been operated with ureteroneocystostomies before the period of the present study), and spontaneously healed reflux in the other can, of course, not be excluded. It is to be noticed, however, that parenchymal changes were rarely found in kidneys belonging to non-refluxing ureters.

The relation between marked reflux and renal parenchymal changes was earlier stressed by several authors (4, 9, 18, 19, 20) and in reports on animal experiments (3). The question cannot yet be answered, however, whether a more marked reflux induces more extensive parenchymal changes or whether both conditions are the consequence of e. g. a specially virulent infection.

It has been reported that in the presence of free reflux, renal changes are

more marked (13). In this study we noticed a tendency in that direction but the phenomenon could not be confirmed because of the small number of kidneys in some of the sub-groups. However, the frequency of free reflux was considerably higher in group A than in group B, indicating that the presence of free reflux renders it less probable that the reflux will heal spontaneously. In group A there were 5 ureters with free reflux and micturition reflux grade 2 or 3 in spite of normal submucosal ureteral segment. Three of the ureters had normal width, 2 were 10 mm wide. The basis of the incompetence of the ureteric orifices in these cases is probably some persisting damage caused by infection (14).

The renal pelvis and the ureter can be distended easily in children. Therefore the width of the ureter is influenced by the examination technique and an exact measurement is impossible. The difference in the ureteric width "at rest" and at reflux or during heavy diuresis may be very great. In most cases, however, the diameter of the refluxing ureters was 4–8 mm "at rest" and in a few cases among the operated patients it was increased to more than 20 mm during reflux.

Due to local oedema, ureteroneocystostomy caused a partial obstruction to the urinary flow distally in the ureter. The obstruction decreased successively during the first postoperative weeks, but it certainly had a temporary effect on the renal haemodynamics and function, as demonstrated in animal experiments (17), the degree depending

on the degree and duration of the partial ureteric obstruction. The intrapelvic pressure was not studied in any case, but even at marked dilatation there was no visible influence on the excretion of contrast medium at urography. This is, however, a rather coarse test of renal function. In one patient, the glomerular function judged from urography decreased successively during the years following operation: this was a boy with gross pyelonephritic changes, bilateral reflux, and reduced renal function present before operation. The excretion of contrast medium also decreased on the non-operated side.

In one of the 2 cases with slight dilatation of the upper urinary tract as late as 12 months postoperatively, the condition is still unchanged after 2.5 years. The dilatation is caused by a slight stenosis distally in the ureter. As judged from urography it has had no harmful effect on the renal function. In the other case the dilatation increased after more than one year following operation. Reoperation was performed 2.5 years later because of a stricture in the most distal part of the ureter. This may imply that one year is too short a time for follow-up studies, especially if the postoperative dilatation of the ureter and pelvis has not fully regressed in due time.

A comparison between the two groups in this study shows that there was gross reflux in 66 per cent in group A and in 10 per cent in group B, and that free reflux was present in 86 per cent in group A and in 23 per cent in

group B. These findings, however, have already influenced to some degree the classification into the two groups. As to the prognosis of the reflux, it can be said that as both groups were subjected to chemoprophylaxis during a certain but varying time, to give the reflux a chance to disappear, the combination of free reflux and marked micturition reflux reduced the chance of spontaneous disappearance of the reflux.

Conclusion and Summary

The following results have been obtained from the roentgenologic examination of 104 children with vesico-ureteric reflux into 145 ureters. All cases received chemoprophylaxis against infection. Sixty-three of the patients (92 ureters) were later operated because of persistent reflux:

Pyelonephritic changes were more extensive and occurred more frequently in cases with marked reflux at micturition, but seemed not to be influenced by the presence or absence of free reflux.

Pyelonephritic changes seldom occurred in kidneys belonging to non-refluxing ureters.

Pyelonephritic changes seldom appeared or progressed when chemoprophylaxis against infection had been started.

The simultaneous occurrence of free reflux, marked reflux during micturition, and parenchymal changes rendered it less probable that the reflux would disappear spontaneously; marked reflux was more common when a submucosal ureteric segment was missing.

Following ureteroneocystostomy, vesico-ureteric reflux could be demonstrated 1 year postoperatively in 2/92 ureters:

Postoperative stenosis distally in the ureter was found in 2 cases. In one case the stenosis appears to be harmless still 2.5 years after operation; in the other, the stenosis appeared first more than 1 year after the operation causing marked hindrance to the urinary flow and calling for reoperation.

The operatively induced dilatation of the upper urinary tract usually disappeared during the first month; where this was not the case, it was later demonstrated that ureteric stenosis had developed.

Except for the case with marked ureteric stenosis mentioned above, operation had no injurious effect on the renal function of parenchyma on either the operated or non-operated side as judged from urography.

Schlußfolgerung und Zusammenfassung

Die im Folgenden angegebenen Ergebnisse wurden mit der Röntgenuntersuchung bei 104 Kindern mit vesiko-ureteralem Reflux in 145 Ureteren erzielt. Alle Fälle bekamen Chemoprophylaxe gegen Infektion. 63 Patienten (92 Ureteren) wurden später wegen persistierenden Refluxes operiert:

Pyelonephritische Veränderungen waren ausgedehnter und stellten sich häufiger ein bei Fällen mit kräftigem Reflux bei der Miktion, schienen jedoch nicht vom Vorhandensein oder Fehlen eines freien Refluxes beeinflusst zu sein.

Pyelonephritische Veränderungen traten selten in Nieren mit refluxfreien Ureteren auf.

Pyelonephritische Veränderungen stellten sich selten ein oder verschlimmerten sich nur selten, wenn eine gegen die Infektion gerichtete, chemoprophylaktische Behandlung eingeleitet war.

Das gleichzeitige Vorkommen eines freien Refluxes, eines kräftigen Refluxes während der Miktion und von parenchymatösen Veränderungen machte es weniger wahrscheinlich, daß der Reflux spontan verschwinden würde; ein kräftiger Reflux war die Regel, wenn ein submuköses Uretersegment fehlte.

Nach der Ureteroneozystostomie konnte 1 Jahr nach der Operation bei 2 von 92 Ureteren ein Reflux nachgewiesen werden:

Eine postoperative Stenose im distalen Ureter wurde bei 2 Fällen gefunden. In einem Fall scheint die Stenose 2 1/2 Jahre nach der Operation harmlos zu sein; in dem anderen Falle trat die Stenose erst über 1 Jahr nach der Operation auf, bedingte eine deutliche Erschwerung des Harnflusses und machte eine Nachoperation erforderlich.

Die operativ bedingte Dilatation des oberen Harntraktes verschwand gewöhnlich während des ersten Monats. Wenn das nicht der Fall war, konnte später erwiesen werden, daß sich eine Ureterstenose entwickelt hatte.

Ausgenommen den erwähnten Fall mit erheblicher Ureterstenose hatte die Operation keine nachteilige Auswirkung auf die Funktion des Nierenparenchyms, weder auf der operierten noch auf der nichtoperierten Seite. Dieser Nachweis wurde durch die Urographie erbracht.

Conclusion et résumé

Les résultats suivants représentent l'analyse radiologique de 104 enfants avec 145 reflux vésico-urétéraux. Tous bénéficièrent d'un traitement chimiothérapeutique anti-infectieux. 63 enfants (c'est-à-dire 92 urétéres) furent secondairement opérés en raison de la persistance du reflux.

Des modifications pyélonéphrétiques importantes se rencontrèrent le plus fréquemment dans les cas de reflux massifs lors de la miction. L'état du parenchyme rénal ne semble pas être influencé par la présence ou l'absence d'un reflux simple.

L'atteinte du parenchyme rénal se rencontre rarement en présence d'un reflux simple.

Les modifications pyélonéphrétiques n'apparaissent ou ne se majorent que rarement en présence d'un traitement anti-infectieux chimiothérapeutique.

La présence d'un reflux, s'aggravant lors de la miction, compliqué de modifications pyélonéphrétiques rend peu vraisemblable sa disparition spontanée. Un reflux massif est de règle en présence d'un segment sous-muqueux urétéral court.

Après urétérocystonéostomie, une année après l'intervention l'auteur mit en évidence deux récives de ces 92 reflux.

De plus il existait deux sténoses postopératoires. Dans un cas, 2 ans 1/2 après l'opération, cette sténose ne semble pas avoir de répercussion. Dans le deuxième cas, la sténose n'apparut que 1 an après l'intervention et provoqua

une gêne fonctionnelle qui nécessite une deuxième intervention.

La dilatation préopératoire des voies urinaires supérieures disparut dans la plupart des cas durant le premier mois après l'intervention. Si après ce délai, cette dilatation subsistait, il fallait en rechercher la cause dans une sténose en développement.

Exception faite du cas ayant nécessité une réintervention, l'auteur n'observa pas de aggravation de la fonction rénale autant du côté opéré que de l'autre. Cette preuve fut fournie par des urographies intraveineuses. *Be*

Conclusiones finales y resumen

Los resultados referidos a continuación fueron obtenidos con exámenes radiológicos de 104 niños con reflujo vésico-ureteral en 145 uréteres. Todos los casos recibieron tratamiento antiinfeccioso preventivo. 63 pacientes debieron ser operados más tarde por reflujo persistente.

Alteraciones pielonefríticas eran más frecuentes y también más extensas en casos con fuerte reflujo durante la micción; sin embargo no parecían ser influidas por la presencia o falta de un reflujo libre.

Eran raras las alteraciones pielonefríticas en riñones cuyos uréteres estaban libres de reflujo.

La aparición o agravación de alteraciones pielonefríticas fueron raras en los casos con profilaxis quimioterápica antiinfecciosa.

La coincidencia de reflujo libre, de fuerte reflujo durante la micción y de alteraciones parenquimatosas, tornaba poco probable la desaparición espontánea del reflujo; un fuerte reflujo era la regla en los casos con falta de un segmento submucoso del uréter.

Después de la uréter-neocistostomía pudo comprobarse reflujo en 2 de 92 uréteres operados, un año después de la intervención.

Una estenosis postoperatoria del uréter distal fué observada en 2 casos. En un caso la estenosis parece ser inofensiva, a dos años y medio de la operación; en el otro caso la estenosis apareció más de un año después de la intervención y produjo una marcada dificultad del flujo urinario, debiendo ser operada.

La dilatación del tracto urinario superior, producida por la operación, desapareció generalmente durante el primer mes del postoperatorio. En caso contrario pudo comprobarse más tarde que se había desarrollado una estenosis ureteral.

Excepto el caso mencionado de estenosis ureteral pronunciada, la operación no tuvo consecuencias perjudiciales sobre la función del parénquima renal del lado operado ni tampoco del lado no operado, como pudo comprobarse mediante la urografía. *Ar*

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RENAL BLOOD FLOW AND FUNCTION DURING NEUROLEPTANAESTHESIA
AND AT ELEVATED INTRAVESICAL PRESSURE

An experimental study in the pig.

Ingemar Helin, Ludvig Okmian and Tord Olin

ABSTRACT

During two hours of neuroleptanaesthesia in five pigs, renal blood flow was unchanged, whereas renal vascular resistance and the mean arterial blood pressure increased. The glomerular function was not significantly altered. The tubular function was moderately impaired.

The intravesical pressure was successively elevated in seven pigs. This caused no changes in renal blood flow. The renal vascular resistance increased paralleled by a slight increase of the mean arterial blood pressure. Both glomerular and tubular function decreased when the intravesical pressure was elevated to 50 mm Hg or above.

Key words: Neuroleptanaesthesia, intravesical pressure, renal blood flow, renal function.

Obstruction to the outflow of urine from the bladder, due to anatomical hindrances or to functional derangements, causes elevation of the pressure within the bladder, and, in the case of vesico-ureteric reflux, within the ureter and renal pelvis. There has been some controversy as to the effects on renal haemodynamics and function of different intravesical pressures. Some investigators have demonstrated an inverse relationship between bladder pressure and urine production (Tolls & Dille, 1955; Prat, 1956) whereas others have been unable to confirm such findings (May & Barelare, 1958). A decrease in glomerular function at elevated intravesical pressure was found by Prat (1956) and Lytton et al (1967). The present experimental study was undertaken primarily to evaluate the responses of the renal blood flow and function of the pig kidney to elevation of the intravesical pressure. In addition, as neuroleptanaesthesia has gained recognition in experimental and clinical practise, it was considered valuable to investigate its effect on the kidney.

MATERIAL

Twelve piglets of the Swedish Land race were used, with a median weight of 16.0 kg. The effects on renal blood flow and function of two hours of neuroleptanaesthesia alone were studied in five animals (Group I) whilst, in the remaining seven animals (Group II), different intravesical pressures were also applied.

METHODS

In Group I (median weight 14.9 kg), measurements of the unilateral renal blood flow (RBF), cardiac output (CO), extraction capacities for $^{51}\text{Cr-EDTA}$ (E_{EDTA}), and $^{125}\text{I-Hippuran}$ (E_{Hipp}) and the mean arterial and mean venous blood pressures (MABP and MVBP, respectively) were made every thirty minutes for two hours.

In Group II (median weight 20.8 kg), the bladder was catheterized and cystography performed to exclude vesico-ureteric reflux. Initial values were obtained for the unilateral renal circulatory and functional parameters at an intravesical pressure of 0 mm Hg. After an equilibration time of

about 20 minutes, the measurements were repeated at intravesical pressures of 10, 25, 50, and 75 mm Hg. The duration of each experiment, from the first measurement to the last, was about two hours.

To measure RBF a catheter in the renal artery was filled with indocyanine-green (Cardio-Green^R, Hynson, Westcott & Dunning Inc., USA) and 0.32 ml dye solution were rapidly injected with the aid of a spring-driven injector (Göthlin & Olin, 1973) modified to hold a disposable 1 ml syringe. To measure CO, four or five ml of the dye solution were rapidly injected through a catheter in the renal vein. Blood samples were obtained from the catheters in the renal vein and the renal artery, respectively. The concentration curve was registered on a potentiometer recorder (Servogor, Goerz, Austria). These techniques have been described in detail by Lingårdh et al (1969), Ekelund et al (1972), and Göthlin & Olin (1973).

Glomerular and tubular function was evaluated by calculating the extraction of $^{51}\text{Cr-EDTA}$ and $^{125}\text{I-Hippuran}$. Two $\mu\text{Ci } ^{51}\text{Cr-EDTA}$ and one $\mu\text{Ci } ^{125}\text{I-Hippuran}$ were mixed with 80 ml of 5.5 per cent glucose and 20 ml PAH solution acting as a carrier. After a priming dose of 1 ml/kg bodyweight a continuous intravenous infusion of this solution was given throughout the experiment at a rate of 0.18 ml/min. Sampling of arterial and venous renal blood was performed slowly and simultaneously after the measurements of RBF and CO had been finished, and the samples were counted in an automatic dual channel well crystal scintillation detector (Selektronik, Denmark) separating radiation from $^{51}\text{Cr-EDTA}$ and $^{125}\text{I-Hippuran}$.

Isotonic heparinized glucose solution was infused at a rate of 1 ml/kg bodyweight/h through one of the ear veins to prevent clotting of the catheters and preclude metabolic acidosis and to maintain a satisfactory diuresis.

Arterial and venous blood pressures were measured through the catheters in the renal artery and renal vein, respectively, by an electromanometer (Siemens-Elema AB, Sweden) and recorded on a polygraph (Mingograf 800, Siemens-Elema AB, Sweden). Blood samples were withdrawn from the renal

artery for the determination of P_{O_2} and acid-base balance (pH, P_{CO_2} , standard bicarbonate and base excess) and haematocrit by a combianalyser (Eschweiler & Co, Kiel, West Germany) and a micromethod (Minor, MSE, England), respectively.

The body temperature of the animal was measured by a rectal thermometer and kept almost constant by insulation and an electric heating pad.

EXPERIMENTAL PROCEDURES

Anaesthesia

All piglets were anaesthetized by an intramuscular injection of ketamine hydrochloride 25 to 45 mg/kg body-weight (Ketalar^R, Parke-Davis, USA; ketaminum NFN) and droperidole 10 to 20 mg/kg body-weight (Dridol^R, Leo, Sweden; droperidolum INN). After intubation, artificial ventilation was given through a respirator with a mixture of 33 per cent O_2 , 66 per cent N_2 , and 1 per cent CO_2 . Alcuronium chloride 0.05 to 0.1 mg/kg body-weight (Alloferin^R, Hoffman La Roche, Switzerland; alcuronium INN) was administered as a muscle relaxant during the experiment.

Operative procedure

The design of the experiment is schematically represented in Fig. 1. Catheterization of one of the renal arteries and the corresponding vein was performed through the femoral vessels with the aid of fluoroscopy. The renal artery was catheterized with a radio-opaque catheter (OPP 160, Portex, England, OD/ID = 1.6/1.15 mm), the tapered and bent tip portion being introduced a short distance into the renal artery. In the renal vein a different type of radio-opaque catheter was used (ÖL 0, Kifa, Sweden, OD/ID = 1.8/1.2 mm) equipped with two side holes near the tip and curved for the distal three to four cm.

The bladder was exposed through a low abdominal midline incision and catheterized with a number 16 or 18 French catheter in seven of the animals (Group II). The catheter was firmly attached to the distal urethra

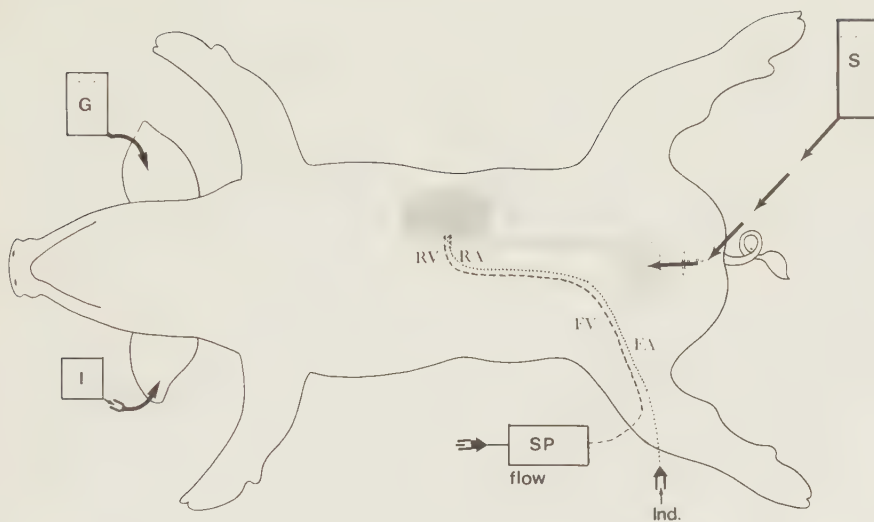


Fig. 1. Schematic drawing of experimental arrangement.

G = glucose
 I = isotopes
 SP = spectrophotometer cuvette
 RV = renal vein
 RA = renal artery
 FV = femoral vein
 FA = femoral artery
 Ind = indicator solution
 S = saline

to avoid leakage. Connection of the catheter to a bottle containing physiological saline enabled different intravesical pressures to be obtained. In all animals urine was withdrawn under sterile conditions for bacteriological analysis.

CALCULATIONS AND STATISTICAL METHODS

RBF and CO were calculated according to the formula:

$$\text{RBF or CO} = \frac{q \times D \times M_{100}}{M} \times 60$$

where RBF = renal blood flow (ml/min) ,

CO = cardiac output (ml/min) ,

q = amount of dye solution injected (ml) ,

D = deflection of the potentiometer recorder when calibrated with 0.1 ml dye in 10 ml blood (cm) ,

M = weight of the excised dye-dilution curve (g) ,

M_{100} = weight of 100 cm² of the same paper (g) .

(For further details of the technique, see Lingårdh et al /1969/).

Each value for RBF is the average of two to four consecutive measurements.

E_{EDTA} and E_{Hipp} were evaluated as described by Lingårdh et al (1970) .

Corrections were made for the background count and for overlap between the channels in the scintillation detector. Glomerular filtration rate (GFR) was expressed as the clearance of ⁵¹Cr-EDTA according to the formula:

$$\text{GFR} = \text{RBF} \times E_{\text{EDTA}} \times \left(1 - \frac{\text{haematocrit}}{100}\right)$$

and expressed in ml/kg body-weight/min.

MABP was calculated as the diastolic pressure plus one third of the pulse pressure and was expressed in mm Hg (1 mm Hg = 0.13333 kilopascal).

The renal vascular resistance (RVR) was calculated according to the formula:

$$\text{RVR} = \frac{\text{MABP} - \text{MVBP}}{\text{RBF}}$$

and expressed in mm Hg/ml/min.

Two-sided analysis of variance, as described by Snedecor & Cochran (1967) was used to estimate the difference between the values obtained at the 5 per cent level of significance.

RESULTS

Group I: Renal blood flow and function during neuroleptanaesthesia.

The results are summarized in Fig. 2, which shows the mean values and standard error of the means for renal circulatory parameters and renal function.

Unilateral RBF and its mean fraction of the cardiac output (RBF % CO) remained fairly stable throughout the experiments. Only minor variations were seen and these were statistically insignificant (Fig. 2:a - b). RVR showed a significant increase during the two hours of neuroleptanaesthesia (Fig. 2:c) as did MABP (Fig. 2:d). The variations of MVBP were minor and statistically insignificant (Fig. 2:e). E_{EDTA} was also insignificantly changed (Fig. 2:f) whereas E_{Hipp} fell continuously, from 64.3 to 51.7 per cent (Fig. 2:g). The estimated GFR fell from 1.9 to 1.4 ml/kg body-weight/min after 60 minutes of neuroleptanaesthesia but remained stable thereafter (Fig. 2:h). Determinations of P_{O_2} and acid-base balance indicated an adequate adjustment of the respirator. The specimens of urine showed no bacterial growth.

Group II: Renal blood flow and function at elevated intravesical pressure.

The results are depicted in Fig. 3, which shows the mean values and standard error of the means for the renal circulatory and functional parameters.

There were no significant changes in RBF, RBF % CO, MABP or MVBP (Fig. 3:a - b, d - e), but the slight increase in RVR was statistically significant (Fig. 3:c).

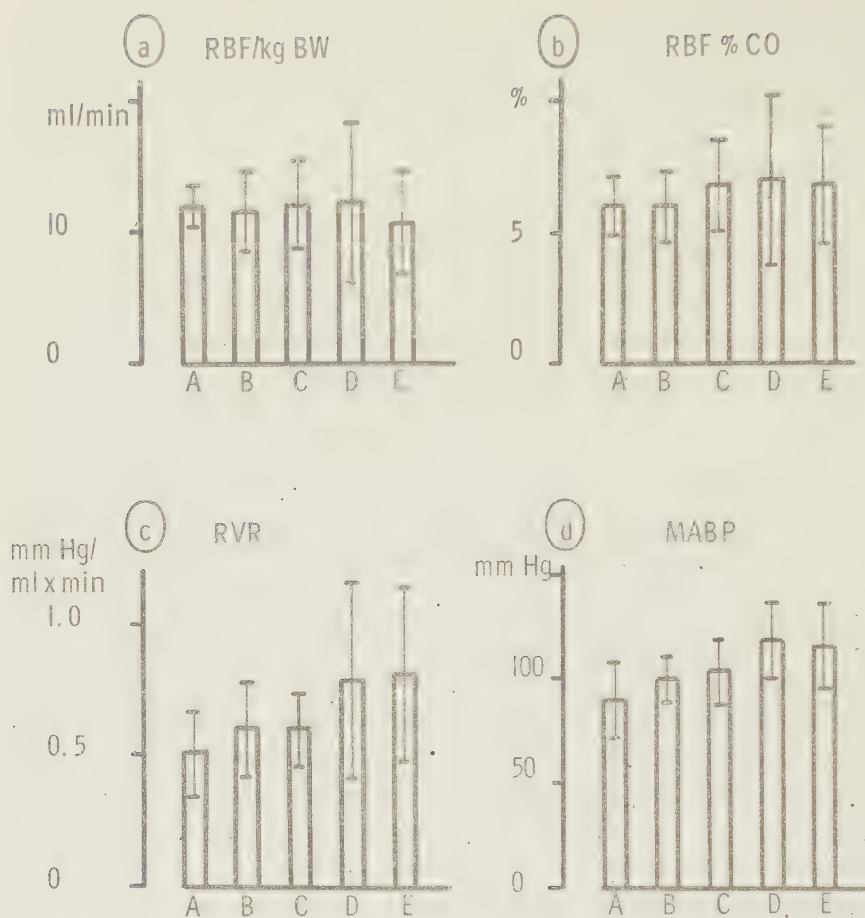


Fig. 2. Parameters of renal blood flow and renal function during neurolept-anaesthesia (Group I).

Unilateral renal blood flow per kg body-weight (RBF), ml/min;

Unilateral renal fraction of cardiac output (RBF % CO), %;

Unilateral renal vascular resistance (RVR), mm Hg/ml/min;

Mean arterial blood pressure (MABP), mm Hg;

The heights of the columns indicate the mean values and the vertical bars the standard error of the means. A = initial values; B = values 30 minutes after A; C = values 60 minutes after A; D = values 90 minutes after A; E = values 120 minutes after A.

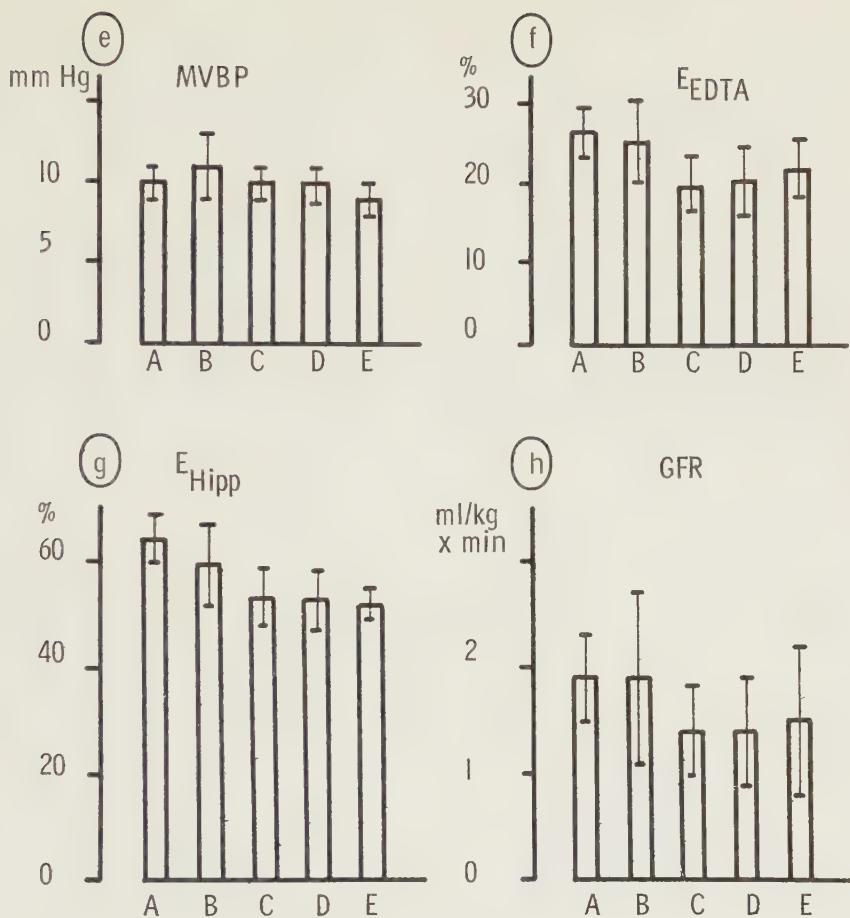


Fig. 2. Parameters of renal blood flow and renal function during neuroleptan-aesthesia (Group I).

Mean venous blood pressure (MVBP), mm Hg;

Extraction of EDTA (E_{EDTA}), %;

Extraction of Hippuran (E_{Hipp}), %;

Glomerular filtration rate (GFR), ml/kg/min.

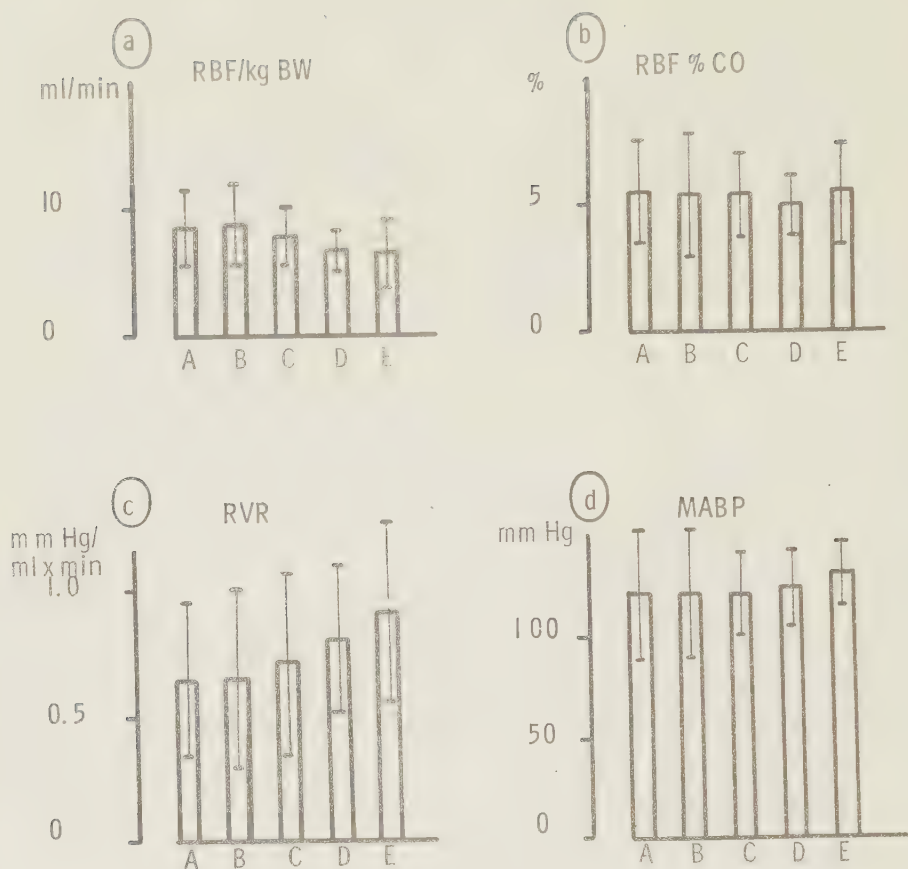


Fig. 3. Parameters of renal blood flow and renal function at elevated intravesical pressure (Group II). A = initial values; B - E = values at an intravesical pressure of 10, 25, 50, and 75 mm Hg, respectively. Abbreviations as in Fig. 2.

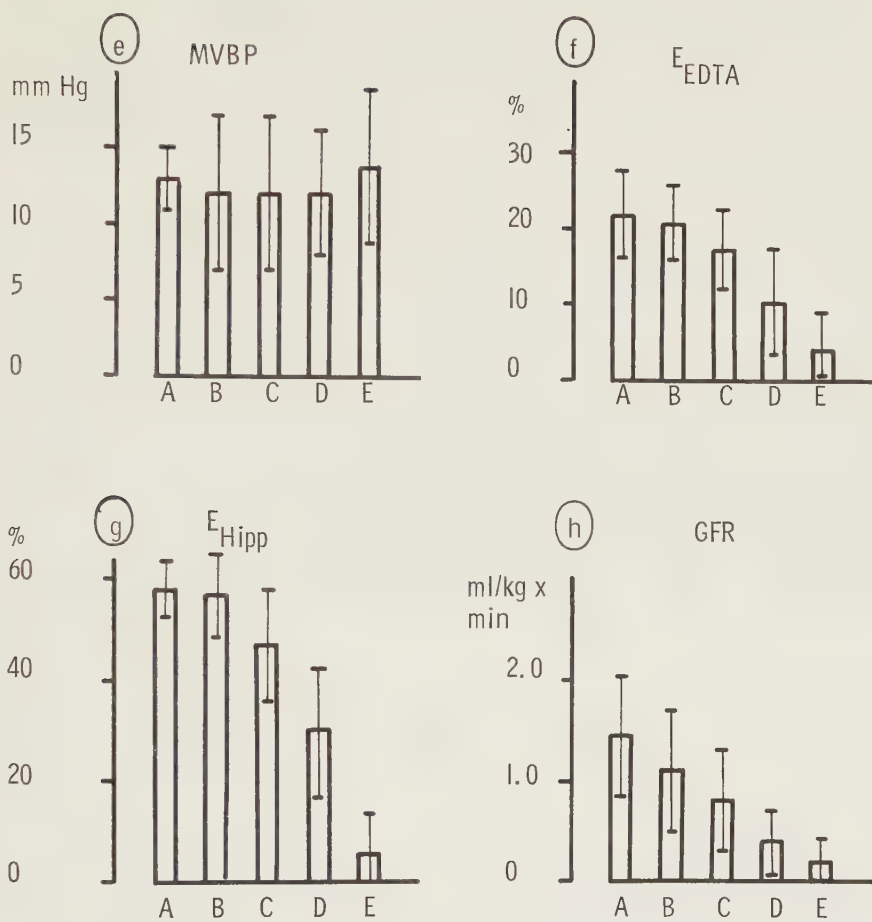


Fig. 3. cont'd.

During elevation of the intravesical pressure E_{EDTA} decreased successively, from 21.8 to 3.9 per cent (Fig. 3:f). E_{Hipp} also fell continuously, from 57.8 to 5.5 per cent (Fig. 3:g). In both cases the main decrease occurred at intravesical pressures of 50 and 75 mm Hg. GFR behaved in a parallel fashion to E_{EDTA} and decreased from 1.2 to 0.2 ml/kg body-weight/min (Fig. 3:h).

The haematocrit values remained fairly constant as did P_{O_2} , P_{CO_2} , pH, standard bicarbonate and base excess.

DISCUSSION

When measuring RBF during anaesthesia it is essential to use a procedure without side effects on the kidney. The values of RBF obtained by the indicator dilution technique have been found to correlate well with those obtained by other methods (Mehrizi & Hamilton, 1959; Jirka et al, 1961; Lingårdh et al, 1969). The basic requirements that must be fulfilled to ensure correct measurements with this technique (e.g. complete admixture of indicator in blood, constant blood flow during the sampling period, exact amount of injected dye and exclusion of the recirculation) have been thoroughly discussed by Lingårdh (1971), Göthlin & Olin (1973), and Lyrdal & Olin (1974) and were taken into account in the present study.

As has been shown by Stacy et al (1966) and Bianchi (1972), the extraction capacity of ^{51}Cr -EDTA provides a reliable measurement of glomerular function, close to that of inulin. In measuring tubular function, the extraction capacity of ^{125}I -Hippuran does not correspond exactly to that of PAH. Lingårdh (1972) found a correction factor of 1.268 between PAH extraction and the extraction of ^{125}I -Hippuran. The lower extraction of ^{125}I -Hippuran did not invalidate its use in the present investigation as only the direction of changes in tubular function was of interest.

Group I: Renal blood flow and function during neuroleptanaesthesia.

It has been shown that different kinds of both inhalation and barbiturate anaesthetics depress RBF (Habif et al, 1951; Papper & Ngai, 1956; Wester-

mark & Wählin, 1969; and others). Nevertheless, experiments performed by Craig et al (1945) and Glauser & Selkurt (1952) caused Selkurt (1963) to conclude that one to two hours of light anaesthesia does not affect the renal circulation, in contrast to prolonged or deep anaesthesia, which would cause a reduction.

In the present study, RBF was unchanged during two hours of neuroleptanaesthesia (Fig. 2:a). We are inclined to ascribe this steady state to the use of non-barbiturates as anaesthetics and analgesics. Droperidole is known to counteract the vasoconstrictor effects of adrenaline and noradrenaline (Tammisto et al, 1973). Although we administered droperidole only as a single intramuscular injection at the start of each experiment, it may, in view of its rather long duration of action (6 to 8 hours), have contributed to the lack of changes in RBF. Vasoconstriction in the kidney, caused by adrenaline and noradrenaline, has been demonstrated by Blake (1955), Aukland (1968) and others, and was presumed to have caused the reduction in RBF observed by Lyrdal & Olin (1974) during pentobarbitone anaesthesia in rabbits.

Ketamine hydrochloride may increase the blood pressure temporarily within 10 to 20 minutes after the injection (Langrehr et al, 1967), a time limit which was respected by us. Alcuronium chloride is not known to cause any disturbance of cardiovascular function (Stovner & Lund, 1964; Hunter, 1968).

The maintenance of renal autoregulation is also substantiated by the finding that, when MABP increased, RBF was unchanged, due to a concomitant increase in RVR (Fig. 2:c - d). It has been supposed (Selkurt, 1964) that renal autoregulation is influenced by anaesthesia, due to activation of the autonomic nervous system. Metabolites formed within the kidney may also influence autoregulation. The changes in RVR in our study were obviously not prevented by the neuroleptanaesthesia. In contrast to the findings of Habif et al (1951) and Lyrdal & Olin (1974), no significant impairment of the glomerular function was observed (Fig. 2:f). Lyrdal & Olin (1974)

suggested that a constriction of the afferent arterioles caused a decrease in the extraction of EDTA. In our study an afferent constriction was substantiated by the decrease of GFR (Fig. 2:h). Tubular function, measured by the extraction of ^{125}I -Hippuran, decreased steadily (Fig. 2:g). The detailed physiological meaning of these functional changes is difficult to analyse in detail. A constriction of the afferent arterioles seems, however, to occur.

Group II: Renal blood flow and function at elevated intravesical pressure.

On elevating the pressure within the bladder, Burton-Opitz & Lucas (1907) registered no effect upon the renal circulation, even when the organ was inflated until it burst. Furthermore, experiments by Lucas (1908) established that a distended bladder with a normal vesico-ureteric junction can have no deleterious effect upon the kidney, unless there exists a nervous pathway. Such a vesicorenal reflex has been the subject of contention. Tolls & Dille (1955) demonstrated an inverse relationship between bladder pressure and urine production by the kidneys even when the ascending column of pressure was interrupted by division of the ureters. May & Barelare (1958) were unable to confirm these findings. Krzeski & Trzebski (1956) observed decreased renal circulation in response to bladder distension and Prat (1956) found not only a suppression of urine flow but also a decrease in glomerular filtration rate and renal blood flow. Experimental results by Langley & Kimura (1959) indicated that section of the hypogastric and pelvic nerves prevented the vesicorenal reflex. On increasing the intravesical pressure, Lytton et al (1967) found a decrease in glomerular filtration when the ureters were cut. Their observations indicated that the reflex was mediated by a neural pathway. In humans, Soloway et al (1972) excluded a nervous reflex via the pelvic and hypogastric nerves.

In our experimental study, no significant changes were observed in RBF or its fraction of the cardiac output (RBF % CO). The results were similar to those in Group I, where the intravesical pressure was unaffected. The increase in RVR (Fig. 3:c) also showed the same pattern, which favours

the supposition that it was caused primarily by the neuroleptanaesthesia rather than by the intravesical pressure. The fact that the changes in MABP in Group II lacked statistical significance may be attributed to a wider variation in the weight and age of the animals than in Group I substantiated by the greater standard error of the mean at 0 and 10 mm Hg (Fig. 3:d).

As regards renal function, the extractions of ^{51}Cr -EDTA and ^{125}I -Hippuran decreased steadily concomitant with the elevation of the intravesical pressure (Fig. 3:f - g). It has been established by Kiil (1957), Boyarsky & Labay (1972) and others, that the maximum ureteric peristaltic pressure is approximately 30 to 40 mm Hg. Accordingly, we found that the main decrease in the extraction capacities occurred at intravesical pressures of 50 to 75 mm Hg. The cessation of the urinary efflux is due to obstruction at the vesico-ureteric junction caused by the increased intravesical pressure. Our results also support findings by Soloway et al (1972) that increased intravesical pressure is transmitted to the kidney when it exceeds the ureteric peristaltic pressure. The tubular pressure increased and the effective filtration pressure diminished due to the stasis of urine.

CONCLUSION

During two hours of neuroleptanaesthesia in the pig, it was found that:

1. renal blood flow and the mean renal fraction of the cardiac output were unchanged,
2. renal vascular resistance increased, as did the mean arterial blood pressure,
3. the glomerular extraction capacity for ^{51}Cr -EDTA was not significantly altered,
4. the tubular extraction capacity for ^{125}I -Hippuran was moderately impaired.

On successively increasing the intravesical pressure during neuroleptanesthesia in the pig, it was found that:

1. renal blood flow and the mean renal fraction of the cardiac output remained unchanged,
2. renal vascular resistance increased significantly whereas a slight increase of the mean arterial blood pressure was insignificant,
3. both glomerular and tubular function, measured by the use of ^{51}Cr -EDTA and ^{125}I -Hippuran, respectively, decreased when the intravesical pressure was elevated to 50 mm Hg or above.

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RENAL BLOOD FLOW AND FUNCTION AT ELEVATED URETERIC
PRESSURE

An experimental study in the pig.

Ingemar Helin, Ludvig Okmian and Tord Olin

ABSTRACT

The unilateral ureteric pressure was successively elevated in five piglets. Bilateral studies of renal blood flow and related parameters (cardiac output, renal vascular resistance, mean arterial and mean venous blood pressures) revealed no significant changes. At a unilateral ureteric pressure of 10 mm Hg, there was a temporary decrease in the renal vascular resistance in both kidneys concomitant with an increase in renal blood flow. Glomerular and tubular function decreased successively as the unilateral ureteric pressure was increased. At a retrograde pressure of 75 mm Hg, some renal function was still preserved, probably due to pyelolymphatic backflow.

Key words: Ureteric pressure, renal blood flow, renal function

Ureteric occlusion for more than 24 hours leads to a gradual decrease in renal blood flow and renal function (Kerr, 1956; Vaughan et al, 1970; Murphy & Scott, 1966). In contrast, acute unilateral ureteric occlusion has evoked variable haemodynamic responses (Gilmore, 1964:a; Hinshaw et al, 1964; Nash & Selkurt, 1964; Thureau, 1964; Vaughan et al, 1971). In some of the studies cited, the kidney was decapsulated (Gilmore, 1964:a) or surgically denervated (Hinshaw et al, 1964; Thureau, 1964), which influenced the results obtained. The present experimental study in the pig was undertaken to investigate the responses of renal blood flow and renal function to elevation of the ureteric pressure without extensive operative procedures of this kind.

MATERIAL

Five piglets of the Swedish Land race were used, with a median weight of 11.4 kg.

METHODS

Cystography was performed by suprapubic puncture of the bladder to exclude vesico-ureteric reflux. Thereafter one of the ureters was catheterized and loaded with different pressures. At each pressure renal blood flow and glomerular and tubular function were measured bilaterally, the contralateral kidney serving as a control. When measuring renal blood flow (RBF), a catheter in the renal artery was filled with indocyanine green (Cardio-Green^R, Hynson, Westcott & Dunning Inc., USA) and 0.11 ml dye solution were rapidly injected with the aid of a spring-driven injector (Göthlin & Olin, 1973). To measure cardiac output (CO), 2.0 ml dye solution were rapidly injected through a catheter in the renal vein. Blood samples were withdrawn from the catheters in the renal vein and renal artery, respectively. The technique has been described thoroughly by Lingårdh et al (1969), Ekelund et al (1972), and Göthlin & Olin (1973). To evaluate glomerular and tubular function, 2 μCi ^{51}Cr -EDTA and 1 μCi ^{125}I -Hippuran were mixed with 80 ml of 5.5 per cent glucose and 20 ml PAH-solution, acting as a

carrier. After a priming dose of 1 ml/kg body-weight, a continuous intravenous infusion of this solution was given throughout the experiment at a rate of 0.18 ml/min. When the measurements of RBF and CO had been finished, samples of arterial and venous renal blood were withdrawn slowly and simultaneously and counted in a dual channel well crystal scintillation detector (Selektronik, Denmark), separating radiation from ^{51}Cr -EDTA and ^{125}I -Hippuran.

The mean arterial and mean venous blood pressures (MABP and MVBP, respectively), were measured as described earlier, as were P_{O_2} and the acid-base balance (P_{CO_2} , pH, standard bicarbonate and base excess) and haematocrit (Helin et al, 1975).

The body temperature of the animal was measured by a rectal thermometer and kept almost constant by insulation and an electric heating pad.

Experimental procedures

Anaesthesia

All piglets were anaesthetized by neuroleptanaesthesia (Helin et al, 1975) and ventilated artificially through a respirator with a mixture of 33 per cent O_2 , 66 per cent N_2 and 1 per cent CO_2 . Alcuronium chloride (Alloferin^R, Hoffman La Roche, Switzerland; alcuronium INN) was administered as a muscle relaxant during the experiment.

Operative procedures

The design of the experiment is schematically represented in Fig. 1. Catheterization of the renal artery and vein was performed bilaterally through the femoral vessels using techniques earlier described (Helin et al, 1975). One of the ureters was exposed through a low abdominal mid-line incision and divided close to the bladder entrance. A number 5 or 8 French catheter was inserted one cm into the ureter and firmly secured by a ligature to avoid urinary leakage. It was verified that there was free urinary flow through the catheter. Connection of the catheter to a bottle containing physiological saline enabled ureteric pressures of 0, 10, 25,



Fig. 1. The design of the experiment.

G = glucose
 I = isotopes
 SP = spectrophotometer cuvette
 RV = renal vein
 RA = renal artery
 FV = femoral vein
 FA = femoral artery
 Ind = indicator solution
 S = saline

50, and 75 mm Hg to be obtained. In all piglets urine was withdrawn under sterile conditions for bacteriological analysis.

CALCULATIONS AND STATISTICAL METHODS

RBF and CO were calculated according to Lingårdh et al (1969) and Helin et al (1975). Each value for RBF is the average of two to four consecutive measurements. The extraction capacities for ^{51}Cr -EDTA and ^{125}I -Hippuran (E_{EDTA} and E_{Hipp} , respectively) were determined according to Lingårdh et al (1970). Corrections were made for the background count and overlap between the channels in the scintillation detector. Glomerular filtration rate (GFR) was expressed as the clearance of ^{51}Cr -EDTA according to the formula:

$$\text{GFR} = \text{RBF} \times E_{\text{EDTA}} \times \left(1 - \frac{\text{haematocrit}}{100}\right)$$

and expressed in ml/kg/min.

MABP was calculated as the diastolic pressure plus one third of the pulse pressure and expressed in mm Hg (1 mm Hg = 0.13333 kilopascal). The renal vascular resistance (RVR) was calculated according to the formula:

$$\text{RVR} = \frac{\text{MABP} - \text{MVBP}}{\text{RBF}}$$

and expressed in mm Hg/ml/min.

Two-sided analysis of variance, as described by Snedecor & Cochran (1967) was used to estimate the difference between the values obtained for the different parameters at the 5 per cent level of significance.

RESULTS

The mean values and standard error of the means for the renal circulatory and functional parameters are depicted in Fig. 2.

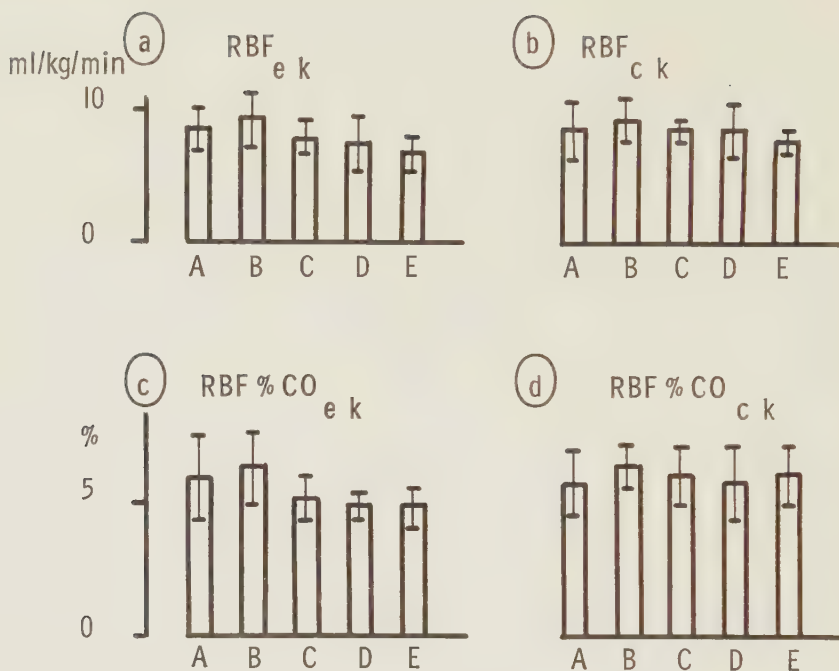


Fig. 2. Parameters of renal blood flow and renal function in experimental kidney (indexed e k) and control kidney (indexed c k).

Renal blood flow per kilo body-weight (RBF), ml/min,

Renal fraction of cardiac output (RBF % CO), %

The heights of the columns indicate the mean values and the vertical bars the standard error of the means.

A = initial values, B - E = values at a unilateral ureteric pressure of 10, 25, 50, and 75 mm Hg, respectively.

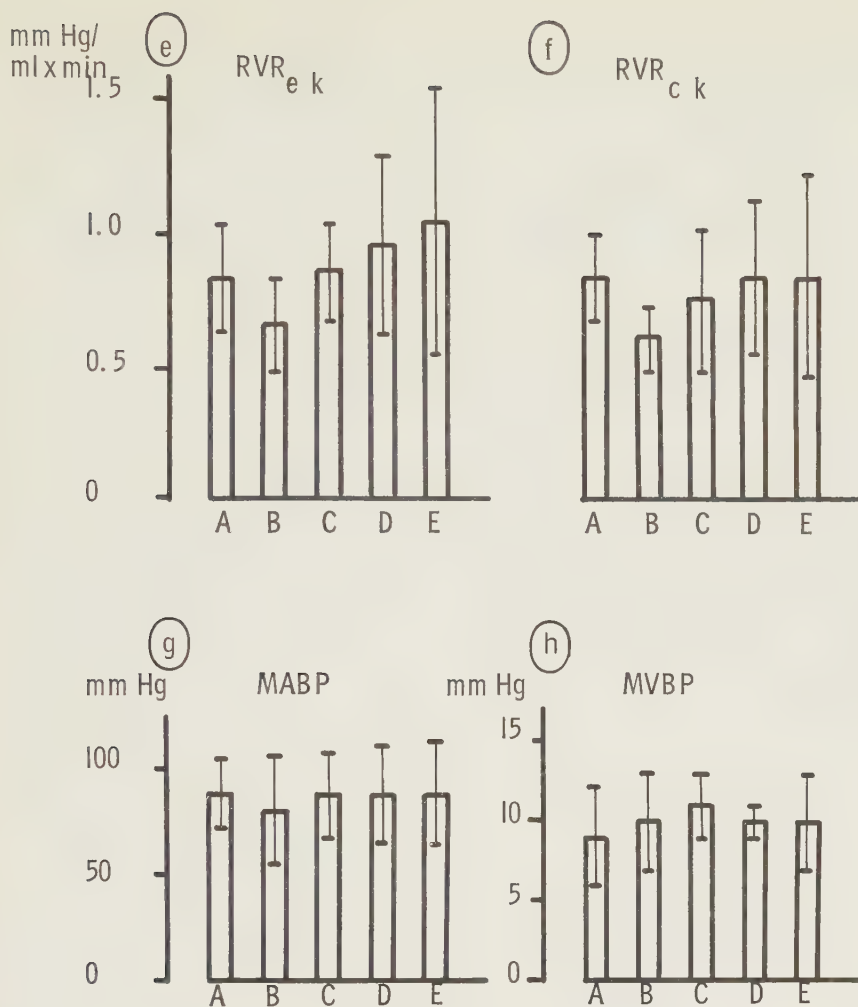


Fig. 2. Parameters of renal blood flow and renal function in experimental kidney (indexed e k) and control kidney (indexed c k)
 Renal vascular resistance (RVR), mm Hg/ml/min,
 Mean arterial blood pressure (MABP), mm Hg,
 Mean venous blood pressure (MVBP), mm Hg

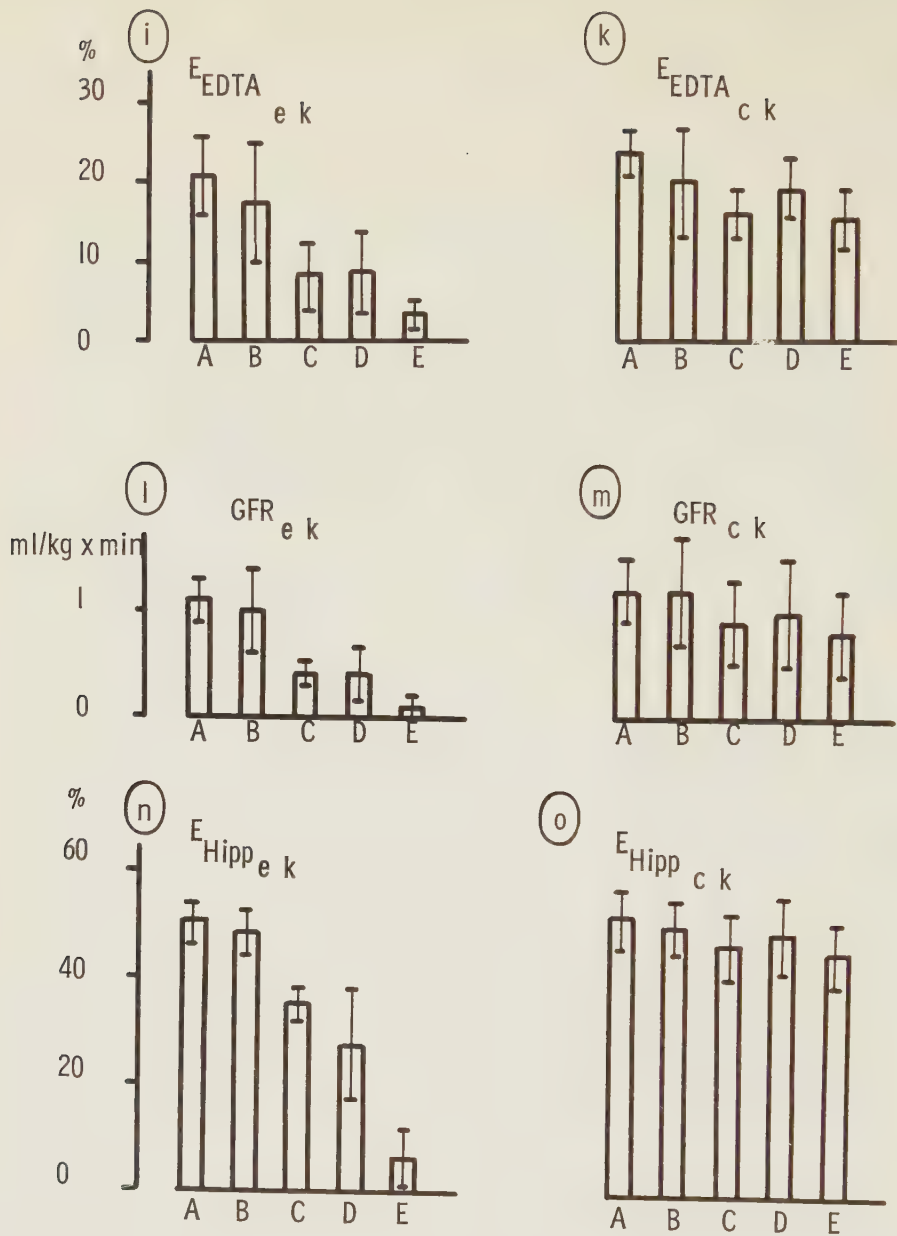


Fig. 2. Parameters of renal blood flow and renal function in experimental kidney (indexed e k) and control kidney (indexed c k)

Extraction of EDTA (E_{EDTA}), %;

Glomerular filtration rate (GFR), ml/kg/min;

Extraction of Hippuran (E_{Hipp}), %.

RBF and the mean renal fraction of the cardiac output (RBF % CO) did not change significantly in either kidney, nor was there any significant difference between the kidneys (Fig. 2:a - d). The variation in RVR, including a bilateral decrease when the pressure in the catheterized ureter was 10 mm Hg, were also insignificant and so was the difference between the kidneys (Fig. 2:e - f). MABP and MVBP exhibited only minor, insignificant fluctuations (Fig. 2: g - h).

Glomerular function, as measured by the capacity to extract ^{51}Cr -EDTA (E_{EDTA}), decreased successively when the pressure in the corresponding ureter was elevated (Fig. 2:i). Irregular variations in E_{EDTA} were observed contralaterally (Fig. 2:k), and the difference between the kidneys was statistically significant. GFR decreased significantly in the kidney subjected to elevated ureteric pressure (Fig. 2:l). Contralaterally, fluctuations similar to those for E_{EDTA} were recorded (Fig. 2:m), and again a significant difference was found between the kidneys. Tubular function, as measured by the capacity to extract ^{125}I -Hippuran (E_{Hipp}) was diminished significantly in the experimental kidney (Fig. 2:n), but only to a minor extent in the contralateral one (Fig. 2:o): the difference between the kidneys was statistically significant. No significant changes were registered in haematocrit values. Determinations of the acid-base balance indicated an adequate adjustment of the respirator. The specimens of urine showed no bacterial growth.

DISCUSSION

It has been shown in other studies that the indicator dilution technique yields reliable values for renal blood flow (for references, see Helin et al, 1975). To ensure correct measurements, however, certain basic requirements must be fulfilled, e.g. complete admixture of indicator in the blood, a constant blood flow during the sampling period, injection of an exact amount of dye and the exclusion of recirculation. These requirements were carefully taken into consideration in the present study.

The technique for producing elevated ureteric pressure has been used by several previous investigators in conjunction with studies of renal blood flow (Gilmore, 1964:a; Nash et al, 1964; and others). It is known that total ureteric occlusion for more than 24 hours will produce a reduction of RBF (Kerr, 1956; Murphy & Scott, 1966; Vaughan et al, 1970) but there is disagreement regarding the haemodynamic responses to acute, unilateral ureteric occlusion of short duration (Gilmore, 1964:a; Hinshaw et al, 1964; Nash & Selkurt, 1964; Thureau, 1964; Vaughan et al, 1971). In the present study, no significant changes were registered in RBF or related parameters (RBF % CO, MABP, MVBP: Fig. 2:a - h). At a unilateral ureteric pressure of 10 mm Hg, however, a temporary decrease in RVR and associated increase in RBF was observed in both kidneys (Fig. 2:a - b, e - f). A similar observation has been made by other investigators (Selkurt, 1963; Gilmore, 1964; Nash & Selkurt, 1964; Thureau, 1964; Murphy & Scott, 1966; Vaughan et al, 1971; and others). After elevation of the unilateral ureteric pressure above 10 mm Hg, RBF and RVR in the experimental kidney showed a transition towards the pattern seen in chronic occlusion, whereas the contralateral RBF and RVR merely normalized (Fig. 2:a - b, e - f).

The reason for the bilateral decrease in RVR at a unilateral ureteric pressure of 10 mm Hg has not been made clear. Vaughan et al (1971) established that it was not mediated by the renal nerves or by circulating catecholamines. The increased ureteric pressure reduces the pressure gradient across the renal vascular bed. When opposed by a proportionate increase in tissue pressure, RVR will fall and a secondary rise in RBF occur (Gilmore, 1964:b). This does not, however, explain the changes in contralateral RVR and RBF. It is possible that prostaglandin E_2 (PGE_2), the major renal prostaglandin (Daniels et al, 1967), is of importance. PGE_2 is a potent renal vasodilator (Lonigro & Terragno, 1973), its release being mediated by angiotensin II (McGiff & Itskovitz, 1973). As PGE_2 is a locally active hormone and removed entirely from the blood on passage across the lung (McGiff & Itskovitz, 1973), it follows that, if the initial resistance to the urinary efflux causes liberation of PGE_2 , then this is secondary to a stimulation of angiotensin II. It has been shown in unilateral renal ischaemia

mia (McGiff & Itskovitz, 1973) that angiotensin II will cause the release of PGE_2 , not only within the kidney subjected to experimentations but also within the contralateral kidney. To pursue the point, maintenance or increase of the unilateral ureteric pressure may well increase the synthesis and release of angiotensin II, so that its direct effect in the ipsilateral kidney comes to override that of PGE_2 and cause vasoconstriction. On the contralateral side, the effects of angiotensin II and PGE_2 are more likely to balance out, leaving RVR at a normal level.

The extraction of ^{51}Cr -EDTA provides a reliable measurement of glomerular function, close to that of inulin (for references, see Helin et al, 1975). The extraction of ^{125}I -Hippuran does not correspond exactly to that of PAH in measuring tubular function. Lingårdh (1972) found a correction factor of 1.268 between PAH-extraction and the extraction of ^{125}I -Hippuran. As we were interested only in the direction of changes in tubular function, the lower extraction capacity for ^{125}I -Hippuran did not invalidate its use in this investigation.

Our finding of a successive reduction in glomerular and tubular function as the ureteric pressure is elevated confirms the observations of Share (1952), and Malvin et al (1964), and others. It was suggested by Share (1952) that the impairment of glomerular function at increased ureteric pressures is due to transmission of the elevated pressure to the nephron lumen, with a consequent reduction in the effective filtration pressure and GFR. In the tubuli there is an active secretion of ^{125}I -Hippuran. It is apparent from this study that the tubular function was less influenced by the increase in ureteric pressure than was the glomerular function. The variations in tubular function, recorded in the kidney that was not subjected to elevated ureteric pressure (Fig. 2:0), were similar to those found when the effects of neuroleptanaesthesia were studied alone (Helin et al, 1975).

As shown by Kiil (1957) and others, the maximum ureteric peristaltic pressure is approximately 30 to 40 mm Hg. At a higher ureteric back-pressure,

the urinary efflux will cease. This might be expected to cause abolition of the glomerular and tubular extraction capacity. In our study, however, some extraction capacity still existed at a ureteric pressure exceeding the maximum peristaltic pressure (Fig. 2;1, n). This preservation of function has also been found by Schirmeister et al (1959), Naber & Madsen (1973), and Lyrdal & Olin (1974). Two explanations have to be taken into consideration: As documented by Hinman (1963), a pyelovenous and tubulovenous backflow exists during ureteric blockade. This backflow, however, drains into the main renal vein and therefore cannot be revealed as an extraction. The basis of a pyelolymphatic backflow has been well established through the work of Kaiserling & Soostmeyer (1939) and Kriz & Dieterich (1970). It has been shown by several investigators (Goodwin & Kaufman, 1956; Murphy et al, 1958; and others) that the lymphatic flow from the kidney increases considerably on obstruction of the urinary outflow. Pyelolymphatic backflow therefore seems to provide the best explanation of the extraction of EDTA and Hippuran observed in this study at ureteric pressures exceeding the peristaltic pressure.

CONCLUSION

On successively elevating the unilateral ureteric pressure in the pig, it was found that:

1. Renal blood flow and associated parameters (renal vascular resistance, mean arterial and mean venous blood pressures and the mean renal fraction of the cardiac output) were not significantly changed.
2. Glomerular and tubular function diminished considerably. At a retrograde ureteric pressure exceeding the ureteric peristaltic pressure, some glomerular and tubular extraction capacity was still preserved, probably due to pyelolymphatic backflow.

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RENAL BLOOD FLOW AND FUNCTION IN VESICO-URETERIC REFLUX

An experimental study in the pig.

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ABSTRACT

A unilateral, free, vesico-ureteric reflux was surgically created in six piglets. Three to four months later, glomerular and tubular function had decreased by about 50 per cent. The reflux also caused a reduction in the kidney's capacity to maintain a steady blood supply when the intra-vesical pressure was elevated.

Key words: Vesico-ureteric reflux, renal blood flow, renal function.

Vesico-ureteric reflux will cause pyelonephritis in the presence of urinary tract infection (for references see Hutch & Amar, 1972; Strohmer, 1974) and is probably a contributing factor in recurrent urinary tract infection due to residual urine in many children (Shand et al, 1970; Helin et al, 1974; and others). Studies of the effects of uninfected vesico-ureteric reflux upon renal function have, however, yielded inconsistent findings (Rowland et al, 1960; Stephens & Lenaghan, 1962; Fritjofsson & Sundin, 1966; King & Idriss, 1967; Hutch & Smith, 1969; Asano, 1970; Lenaghan et al, 1972; Newman et al, 1974; and others). We therefore felt it important to investigate the long-term effects of a free and uninfected vesico-ureteric reflux upon renal blood flow and function in the growing animal.

MATERIAL

Six piglets of the Swedish Land race were used, weighing 4.3 to 4.8 kg at the beginning of the investigation.

METHODS

The preparation of the animals for the measurement of renal blood flow (RBF), cardiac output (CO), and glomerular and tubular function was identical to that in previous investigations (Helin et al, 1975:a, b). Blood flows were measured by an indicator dilution method using indocyanine green (Cardio-Green^R, Hynson, Westcott & Dunning Inc., USA) as the indicator. To obtain unilateral RBF, 0.32 ml of the dye solution was injected into the renal artery and blood was sampled from the corresponding vein. When measuring CO, 5.0 ml of the dye solution were rapidly injected into a renal vein and blood was sampled from one of the renal arteries. The arterial and venous blood pressures (MABP and MVBP, respectively) were recorded by electromanometry after each flow measurement. The radiochemicals, ⁵¹Cr-EDTA and ¹²⁵I-Hippuran, were dissolved in isotonic glucose solution and infused intravenously throughout the experiment. Samples of arterial and renal venous blood were withdrawn slowly and simultaneously after every flow recording to enable measurement of the extraction capacities (Helin et al, 1975:a).

Samples of arterial blood were also taken for the determination of P_{O_2} and acid-base balance (pH, P_{CO_2} , standard bicarbonate and base excess) and haematocrit. The body temperature was measured by a rectal thermometer and kept almost constant by insulation and an electric heating pad. Urinary specimens were cultured twice during the existence of reflux.

EXPERIMENTAL PROCEDURE

The animals were anaesthetized with ketamine hydrochloride (Ketalar^R, Parke-Davis, USA; Ketaminum NFN) 40 to 50 mg/kg body-weight and droperidole (Dridol^R, Leo, Sweden; droperidolum INN) 2.0 to 2.5 mg/kg body-weight. A unilateral vesico-ureteric reflux was created as described by Ross & Thompson (1963) and others: With the animal lying on its back, the bladder was exposed and opened in the midline just above the bladder neck, and the intravesical portion of one of the ureters was catheterized and entirely divided. The edges of the divided ureter were sutured to the bladder mucosa. The bladder was closed and 0.9 g bensylpenicillin (Gonocillin^R, Leo, Sweden; bensylpenicillinum INN) was given intramuscularly to prevent wound infection.

Three weeks later, the occurrence of a free, unilateral reflux was verified at cystography, performed by suprapubic puncture of the bladder. The roentgen contrast medium, containing 50 mg iodine per ml, was allowed to drip slowly into the bladder. Free reflux was defined as reflux of contrast medium into the ureter and the renal pelvis at an intravesical pressure of 25 mm Hg or less. Three to four months after the operation, the occurrence of free reflux was verified again. Thereafter, studies of bilateral renal blood flow and function were performed at successively elevated intravesical pressure by the procedures earlier described (Helin et al, 1975:a). The median weight of the animals at this time was 40.5 kg. Neuroleptanaesthesia, supplemented with alcuronium chloride (Alloferin^R, Hoffman La Roche, Switzerland; alcuronium INN) as a muscle relaxant, was used to keep the animals lightly anaesthetized (Helin et al, 1975:a).



Fig. 1. Schematic drawing of experimental arrangement.

G = glucose
 I = isotopes
 SP = spectrophotometer cuvette
 RV = renal vein
 RA = renal artery
 FV = femoral vein
 FA = femoral artery
 Ind = indicator solution
 S = saline

The design of the experiment is schematically represented in Fig. 1 and the procedures performed are summarized in Table I.

CALCULATIONS

RBF and CO were calculated as described by Lingårdh et al (1969). Each value for RBF is the average of two to four consecutive determinations. Measurements of the extraction capacities for ^{51}Cr -EDTA (E_{EDTA}) and ^{125}I -Hippuran (E_{Hipp}) were made according to Lingårdh et al (1970). Corrections were made for the background count and overlap between the channels in the scintillation detector. Glomerular filtration rate (GFR) was calculated according to the formula:

$$\text{GFR} = \text{RBF} \times E_{\text{EDTA}} \times \left(1 - \frac{\text{haematocrit}}{100}\right)$$

and expressed in ml/kg/min.

MABP and renal vascular resistance (RVR) were calculated as previously described (Helin et al, 1975:a).

Two-sided analysis of variance, as described by Snedecor & Cochran (1967) was used to estimate the difference between the values obtained at the 5 per cent level of significance.

RESULTS

The mean values and standard error of the means for the renal circulatory and functional parameters are summarized in Fig. 2. In the kidneys subjected to long-term vesico-ureteric reflux, significant alterations in RBF occurred at elevated intravesical pressures (Fig. 2:a) whereas, in the contralateral kidneys, RBF was unchanged (Fig. 2:b). The difference between the kidneys was statistically significant. Although changes in the mean unilateral renal fraction of the cardiac output ($\text{RBF} \% \text{CO}$) were not significant on either side (Fig. 2:c - d), an instability was notable in kidneys with a refluxing ureter (Fig. 2:c). As a rule, RVR increased in both kidneys when the intravesical pressure was elevated (Fig. 2:e - f). Only minor variations of MABP and MVBP were recorded (Fig. 2:g - h). The

TABLE I. Survey of procedures performed in six piglets

Number of animals examined at intravesical pressures of		Type of examination
0, 10, 25, 50 mm Hg	75 mm Hg	
6/6	3/6	Renal blood flow Cardiac output Mean arterial blood pressure Clearance of ⁵¹ Cr-EDTA
6/6	4/6	Extraction capacity for ⁵¹ Cr-EDTA Extraction capacity for ¹²⁵ I-Hippuran
3/6	3/6	Mean venous blood pressure Renal vascular resistance

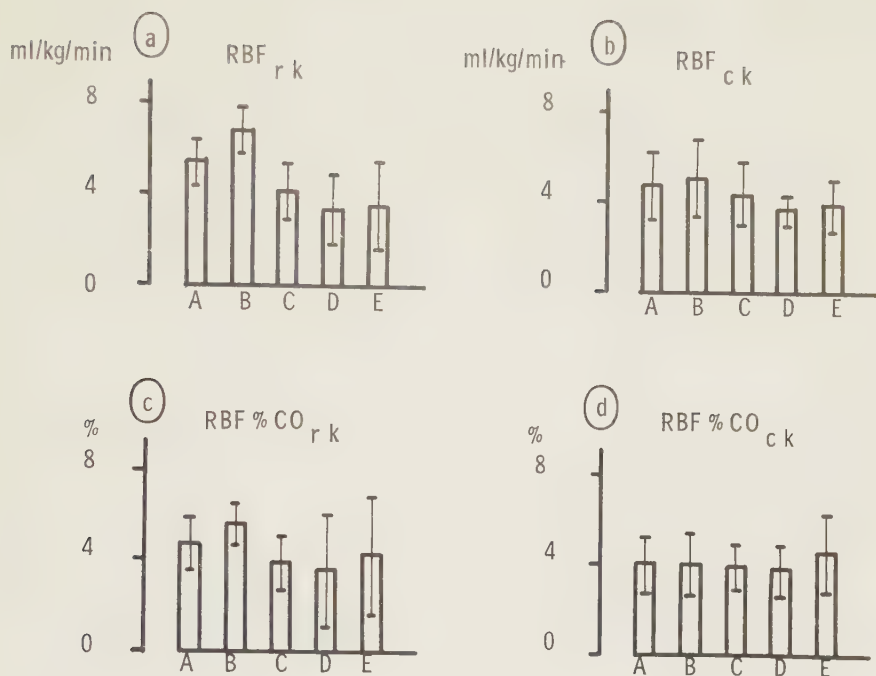


Fig. 2. Parameters of renal blood flow and renal function in reflux kidney (indexed r k) and control kidney (indexed c k).

Renal blood flow per kg body-weight (RBF), ml/min;

Renal fraction of cardiac output (RBF % CO), %;

The heights of the columns indicate the mean values and the vertical bars the standard error of the means.

A = initial values, B - E = values at an intravesical pressure of 10, 25, 50 and 75 mm Hg, respectively.

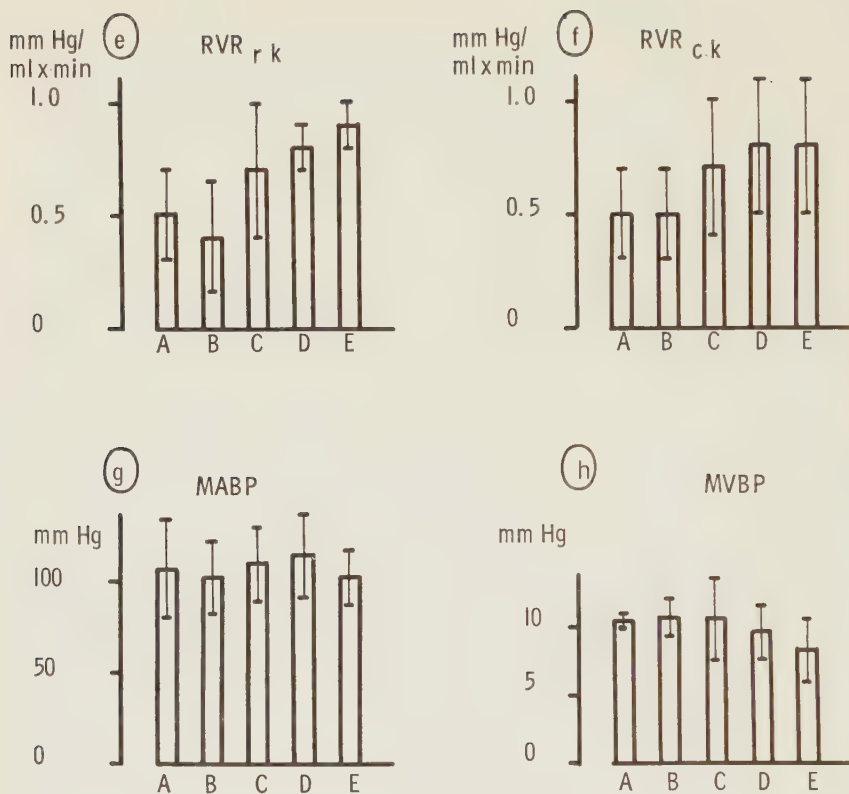


Fig. 2. Parameters of renal blood flow and renal function in reflux kidney (indexed r k) and control kidney (indexed c k).
 Renal vascular resistance (RVR), mm Hg/ml/min;
 Mean arterial blood pressure (MABP), mm Hg;
 Mean venous blood pressure (MVBP), mm Hg;

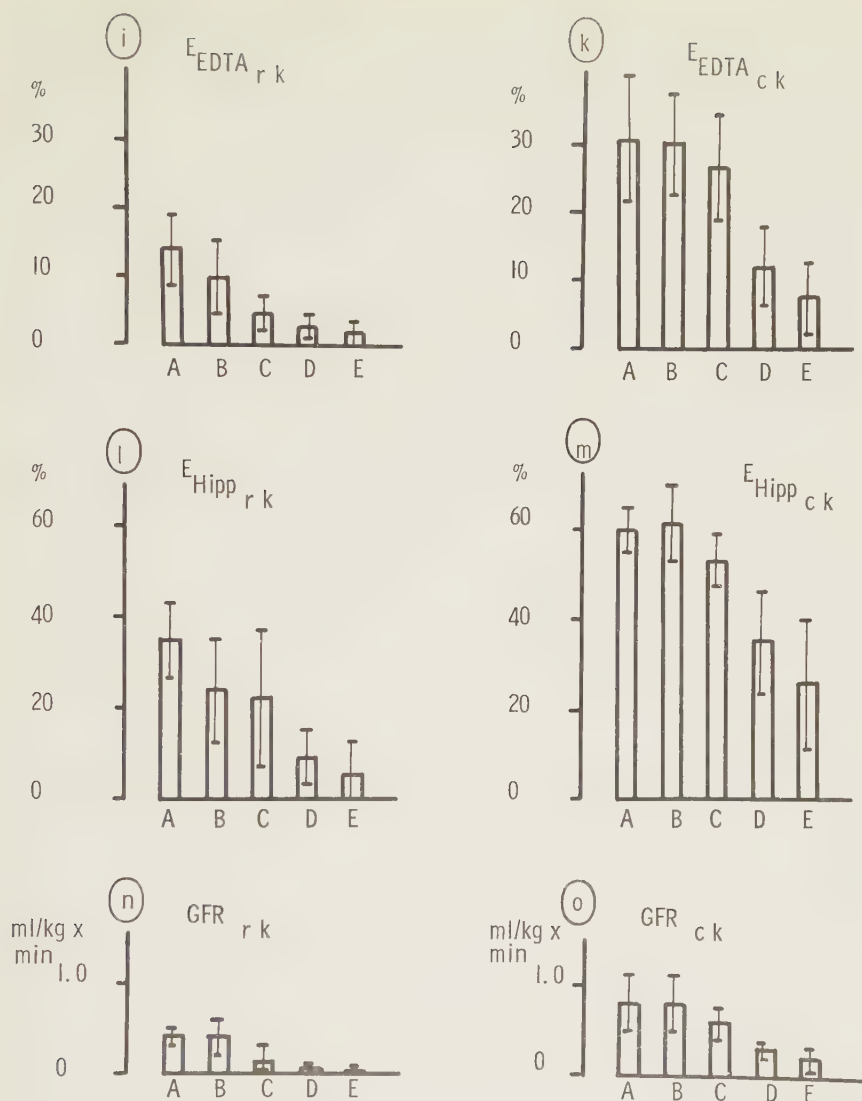


Fig. 2. Parameters of renal blood flow and renal function in reflux kidney (indexed r k) and control kidney (indexed c k).

Extraction of EDTA (E_{EDTA}), %;

Extraction of Hippuran (E_{Hipp}), %;

Glomerular filtration rate (GFR), ml/kg/min.

extraction of ^{51}Cr -EDTA was significantly reduced bilaterally (Fig. 2:i - k) when the intravesical pressure was elevated, this reduction being more accentuated in kidneys with a refluxing ureter. The extraction of ^{125}I -Hippuran also fell continuously and bilaterally when the intravesical pressure was elevated (Fig. 2:l - m). However, in kidneys subjected to a long-term, free, vesico-ureteric reflux, the initial values for the glomerular and tubular extraction capacities, were, respectively, 54 and 42 per cent lower than normal. Furthermore, glomerular function, as judged from the glomerular filtration rate, was significantly reduced on both sides (Fig. 2:n - o). This reduction was more accentuated in kidneys with a refluxing ureter, where the initial values, corresponding to an intravesical pressure of 0 mm Hg, were 50 per cent lower than normal. Haematocrit, P_{O_2} and acid-base balance were unchanged.

The urinary specimens showed no bacterial growth either three weeks or three to four months after the unilateral reflux had been created.

DISCUSSION

The determinations of RBF and CO in this study were made by the indicator-dilution technique, as used by previous investigators (for references, see Helin et al, 1975:a). It does not require dissection of the renal vessels or of the renal pedicle, and was therefore considered to be the most appropriate method. The influence upon the circulatory and functional parameters of neuroleptanaesthesia alone and elevation of the intravesical and ureteric pressure per se has been the subject of separate investigations (Helin et al, 1975:a, b).

It was seen in this study (Fig. 2:a - b) that when the intravesical pressure was elevated, the blood flow to the kidney subjected to a long-term, free, vesico-ureteric reflux was more unstable than that to the contralateral kidney. Apparently, the free reflux had caused a reduction in the capacity of the corresponding kidney to maintain a steady blood supply on elevation of the retrograde pressure. In contrast to these findings,

RBF was unchanged when, in a previous study, the ureteric pressure was elevated without pre-existing reflux (Helin et al, 1975:b). It should also be noted that no compensatory increase in RBF developed in kidneys with a competent vesico-ureteric junction (Fig. 2:b).

It is known that RBF to some extent follows changes in CO (Lyrdal & Olin, 1974; and others), which commonly exhibits fluctuations during an experimental study. Therefore it was considered of interest to express RBF also as a percentage of CO (RBF % CO). No statistically significant changes were observed in this ratio, although some variations in kidneys with a refluxing ureter (Fig. 2:c) followed the same pattern as RBF (Fig. 2:a). This may speak in favour of the supposition that the hydrodynamic effect of a free reflux will reduce the capacity of the corresponding kidney to maintain a constant blood supply.

RVR changed bilaterally when the intravesical pressure was elevated (Fig. 2:e - f). The changes were identical in both kidneys except at an intravesical pressure of 10 mm Hg, when a slight decrease was noticed in kidneys with a refluxing ureter (Fig. 2:e). A similar result was obtained in an earlier study of renal haemodynamics at elevated ureteric pressure without pre-existing reflux (Helin et al, 1975:b).

The most striking effects of the prolonged, free and uninfected unilateral reflux were those upon glomerular and tubular function. After three to four months of free reflux, the extraction capacities of the corresponding kidneys were approximately 50 per cent less than normal (Fig. 2:i - m). The glomerular function decreased steeper at elevated intravesical pressure than did the tubular function. This may be explained by the fact that filtration within the glomeruli depends only on the pressures on each side of the basal membrane, whereas in the tubuli there is an active secretion. The decrease in glomerular function was also substantiated by an initially low glomerular filtration rate (Fig. 2:n). It thus appears that a free and uninfected vesico-ureteric reflux is not as harmless to the kidney as has been supposed by most other investigators (Stephens & Lenaghan, 1962;

King & Idriss, 1967; Lenaghan & Cussen, 1968; Lenaghan et al, 1972; May et al, 1973; Newman et al, 1974). It is therefore worth noting that Rowland et al (1960) in a study of 16 cord injury patients, found that nine of them had differences in renal function, the poorer kidney being in all cases subjected to vesico-ureteric reflux. There was no correlation between the decrease in function and the number of past urinary tract infections. Asano (1970) registered delayed excretion in the ^{131}I -radio-renogram in kidneys with a refluxing ureter. As no operative treatment was undertaken to eliminate the reflux in our animals, it was not possible to determine whether or not the changes in renal blood flow and function were reversible.

CONCLUSIONS

Six piglets were studied after three to four months with a surgically created, unilateral, free, vesico-ureteric reflux. No urinary tract infection was observed. Determinations of renal blood flow indicated that the reflux had caused a reduction in the capacity of the corresponding kidney to maintain a steady blood flow when the intravesical pressure was elevated. The glomerular and tubular function, as measured by the extraction for ^{51}Cr -EDTA and ^{125}I -Hippuran, respectively, had decreased by about 50 per cent. The results of this experimental study imply that a long-term, free, and uninfected vesico-urèteric reflux will reduce glomerular and tubular function and even, to some extent, interfere with the renal circulation.

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